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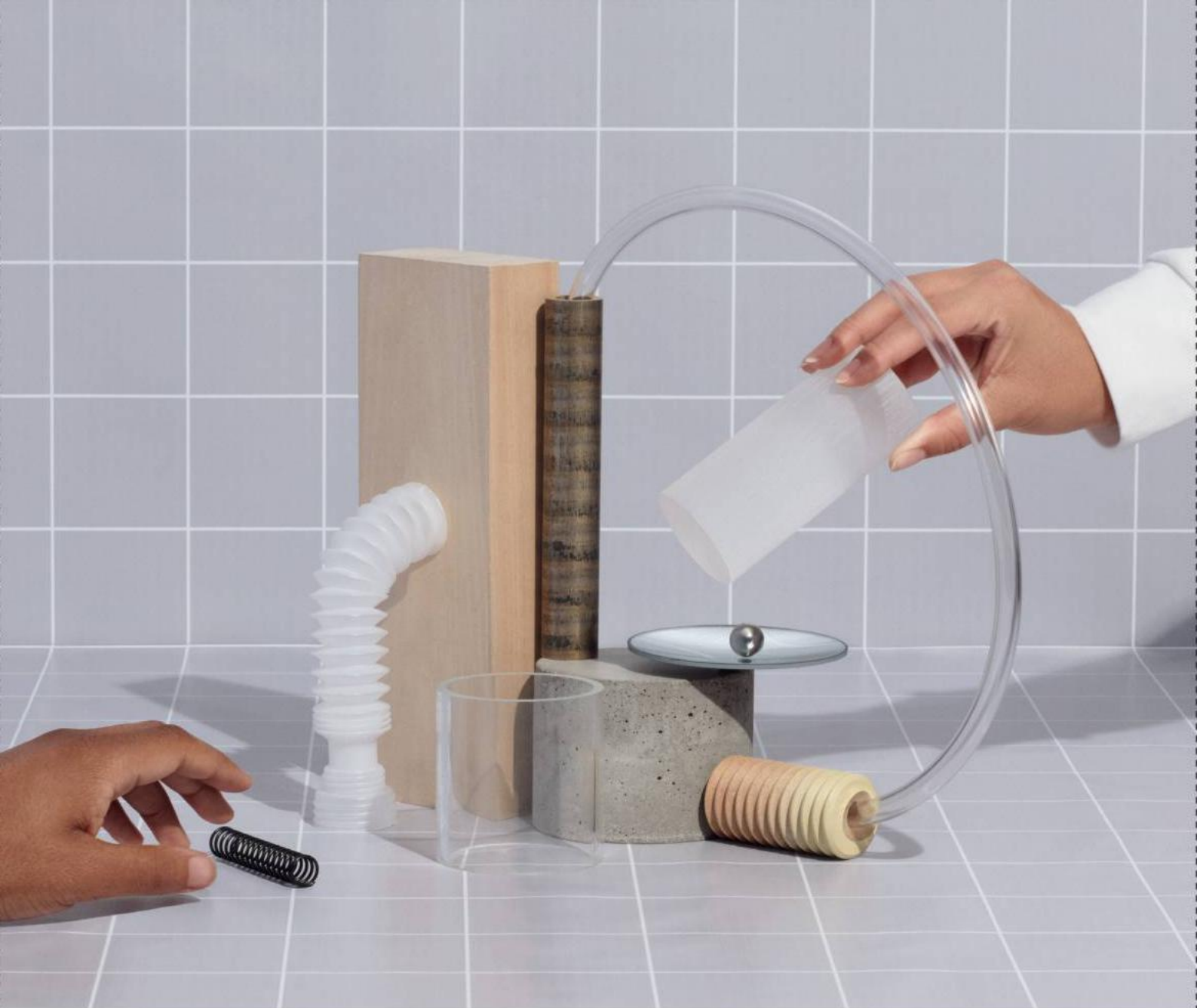


WHAT'S IN WILDFIRE SMOKE? // HOW WE LEARN // NEW HOPE FOR RARE DISEASES

A COSMIC CRISIS

How fast is the
universe expanding?
Scientists can't
agree—and that's
a problem





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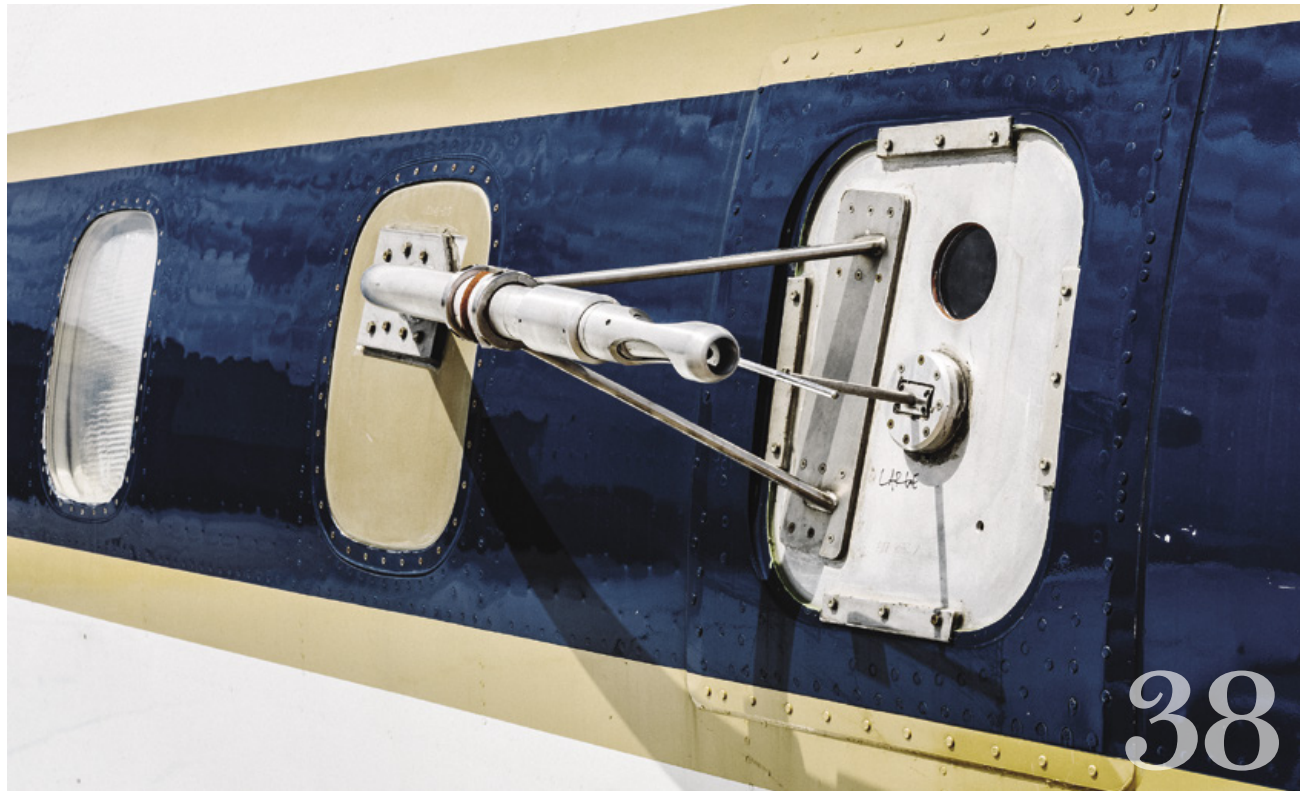
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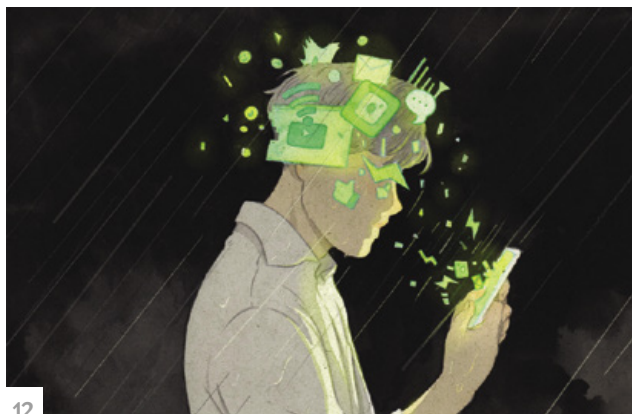
Neuroscientists have discovered a set of unfamiliar cellular mechanisms for making fresh memories. *By R. Douglas Fields*



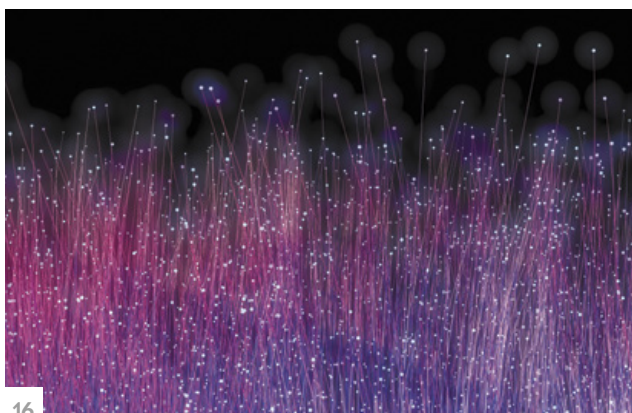
ON THE COVER

The value of the Hubble constant—the rate of the universe's expansion—may be the most important number in all of cosmology. Yet measurements of it from the “early” universe shortly after the big bang and the “late” universe of today disagree. Resolving this discrepancy could lead to a scientific revolution. Illustration by Mark Ross Studios.

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Curtis Brainard is acting editor in chief of *Scientific American*. Follow him on Twitter @cbrainard

Troubled Times

“Crisis” is a strong word. Just a few weeks before this issue went to press, the U.S. and Iran seemed to be on the brink of war. So it might seem excessive to define a situation in which there is no danger to life or limb as a crisis. But in the world of cosmology, there may be no greater predicament than two divergent measurements of how fast the universe is expanding.

Last July, when scientists gathered at the Kavli Institute for Theoretical Physics in Santa Barbara, Calif., to discuss the incongruity, “crisis” was the label they chose. Award-winning author Richard Panek explains the logic in his coverage of the expansion research, starting on page 30: “Unlike a tension, which requires a resolution, or a problem, which requires a solution, a crisis requires a wholesale rethink. But of what?” In this case, it could be the measurement based on observations of the early universe using the cosmic microwave background, the measurement based on observations of the late universe using so-called standard candles, or the standard cosmological model itself. So, a crisis it is.

Elsewhere we turn our attention to more familiar, life-threatening examples of that classification. Beginning on page 38, journalist Kyle Dickman chronicles atmospheric chemists’ efforts to understand what dangers lurk in wildfire smoke. As a result of climate change, such blazes now happen in places they once didn’t, and they’re more intense in places where they’ve always been. Disturbingly, we still don’t know how their emissions might imperil human health, but a project called FIREX-AQ is seeking to redress that ignorance.

Next, a pair of articles examine a form of genetic therapy that relies on antisense oligonucleotides—short strings of chemically modified DNA and RNA that incite or inhibit protein production to thwart pathology. First, journalist and *Scientific American* contributor Lydia Denworth (page 46) and then married medical researchers Sonia Minikel Vallabh and Eric Vallabh Minikel (page 54) describe applications for rare neurodegenerative diseases. Both stories are poignant—respectively, they recount the impacts of these illnesses on children and the researchers themselves (Vallabh carries a DNA mutation that puts her at grave risk for prion disease)—but also full of hope and determination in the face of adversity.

Finally, after a piece by science writer Gabriel Popkin, “What Is Killing the Monarchs?” (page 60), that lays out a new view of what is afflicting America’s most beloved butterfly, we break from crisis with rousing coverage of natural history and neuroscience.

Scientific American senior editor Kate Wong tells a tale (page 68) about the discovery of what may be the oldest known example of narrative art—a 40,000-year-old cave painting of a hunt found on the island of Sulawesi in Indonesia. Following that, on page 74, neuroscientist R. Douglas Fields writes the sequel to his 2008 article for this magazine about the surprising revelation that the brain’s white matter (once thought to be merely structural) plays an important part in learning. Now Fields and others have figured out exactly how glial cells alter myelin, the insulation of our neural wiring, to support the mind’s acquisition of knowledge.

In every issue, we strive for this balance between great crises in science and society and great strides in research. What the stories have in common is the power to fascinate and inspire. ■

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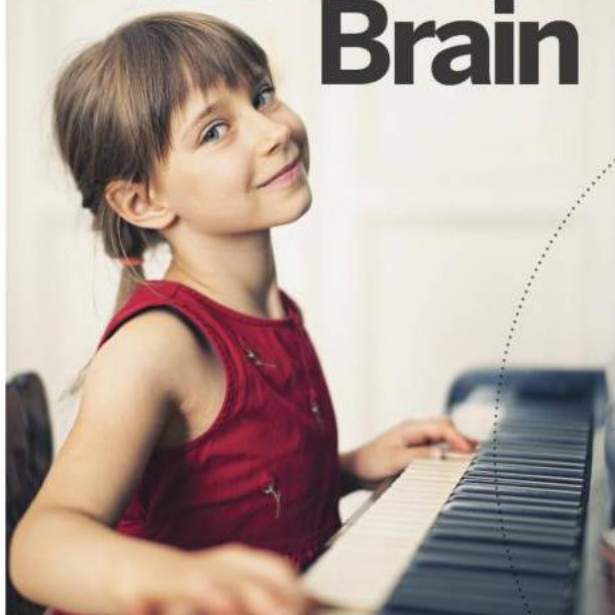
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November 2019

SOCIAL MEDIA DEBATE

Lydia Denworth is a little too quick to dismiss fears of the effects of social media on young people by setting up false equivalences in “The Kids Are All Right.” For instance, if fears of television have been unfounded, it doesn’t follow that fears of social media are parallel in a meaningful way. And I don’t think either that example or the others she cites have been unequivocally proved to be baseless. I thought it was fairly well established that too much TV is bad for developing minds. Further, one could easily build a case that city life (at least a congested one disconnected from a stable community) is comparatively detrimental to mental well-being. And clearly, Socrates was correct that the use of writing would affect the ancient practice of memorization: it’s unlikely anyone today would be able to recite the *Iliad* in its entirety.

JON FRAZE *via e-mail*

I find that one result of the growing use of social media is seldom addressed: When young people use it as their chief way to communicate, it seems they lose the ability to “read between the sentences.” How does one learn to decipher body language or hear expressions of joy, despair, fear or distress when reading texts? How does one express the depth of gratitude in the shortened and misspelled phrase “Thanx”? I fear that what will be lost is a richness of the spoken word and the subtlety of

“We have not only a national mental health crisis but also a *global* one.”

DAVID DEREZOTES UNIVERSITY OF UTAH

thoughts gained only through hearing nuanced sentences.

JOAN MCCRACKEN *Billings, Mont.*

IMPROVING MENTAL HEALTH

Kirk J. Schneider has great points about how we might benefit from a new kind of national leadership to tackle our mental health crisis in “The U.S. Needs a Mental Health Czar” [Forum]. As a social worker and social work and mental health educator, I would like to also add a few more ideas to the discussion.

First, rather than having a single czar who is an expert on *psychological* approaches, we might consider the possibility of introducing a *multidisciplinary team* that would consider many interrelated factors we now suspect are associated with mental health. For example, social workers could add much to the assessment of, prevention of and response to mental illness by considering environmental factors that may contribute to the suffering of people today. Similarly, ecological scientists and biologists might, for instance, be able to help us understand how air pollution, traffic congestion and other urban stressors could be associated with human problems. And the addition of people who are skilled at assessing spiritual needs might also contribute. Such a team could be especially helpful in the *primary prevention* of mental illness through building new regulations, policies and social justice reforms.

Second, we have not only a national crisis but also a *global* one. For example, the widespread depression of individuals across the globe that the World Health Organization has repeatedly noted may reflect, at least in part, a reaction to such issues as climate change, displacement and preparations for war. Because the biological and psychological welfare of people in our country is interrelated with that of everyone else on our “shrinking” planet, the U.S. could work collaboratively with other

nations to identify factors that may contribute to all human suffering.

DAVID DEREZOTES *University of Utah*

COIN LOSS

In “The Inescapable Casino,” Bruce M. Boghosian presents a scenario in which “Shauna” gambles on coin tosses. Each win increases her wealth by 20 percent, and each loss decreases it by 17 percent. It seems to me that the result of the simulation is implicit in the way it is set up: If Shauna’s wealth is \$100 and she plays against a richer agent, then one win, followed by one loss, or vice versa, results in a net loss to her of \$0.40, or 0.4 percent of her initial wealth. If she plays against a less wealthy agent, then she will gain 0.4 percent of that agent’s wealth. Thus, the net gain always flows to the wealthier agent. A 20 percent win and 17 percent loss do not represent a fair system. And replacing the latter with anything greater than $16\frac{2}{3}$ percent will produce the same results.

JAMES LYSENKO *Montreal*

BOGHOSIAN REPLIES: *Lysenko’s calculations are correct. In the yard sale model my scenario was based on, the fractions won and lost with each coin flip are the same, which even more clearly favors the wealthier agent. In the case where Shauna is the poorer agent, I decreased her loss percentage to emphasize that even when she has a positive expected gain at each flip, the longer she plays, the more likely she is to lose.*

To underscore Lysenko’s point with simpler numbers, let’s change the poorer agent’s win and loss percentages to +100 and –75, respectively. Her expected gain in wealth is now $(100\% - 75\%) / 2 = 12.5\%$, which is positive. But note that winning means doubling her wealth, and losing means quartering it. Hence, it takes two wins to compensate for a single loss. Because the coin is fair, she will lose in the long run, even though her expected gain in wealth at each toss is positive.

A different way to frame this apparent paradox is to note that the expected gain in the logarithm of the poorer agent’s wealth is negative. Supposing that we use base 2 logarithms: If she wins, her wealth is doubled, so its logarithm increases by 1. If she loses, her wealth is quartered, so its logarithm decreases by 2. Thus, the expected



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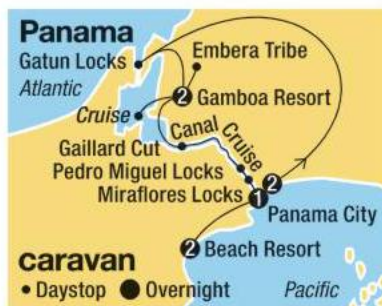
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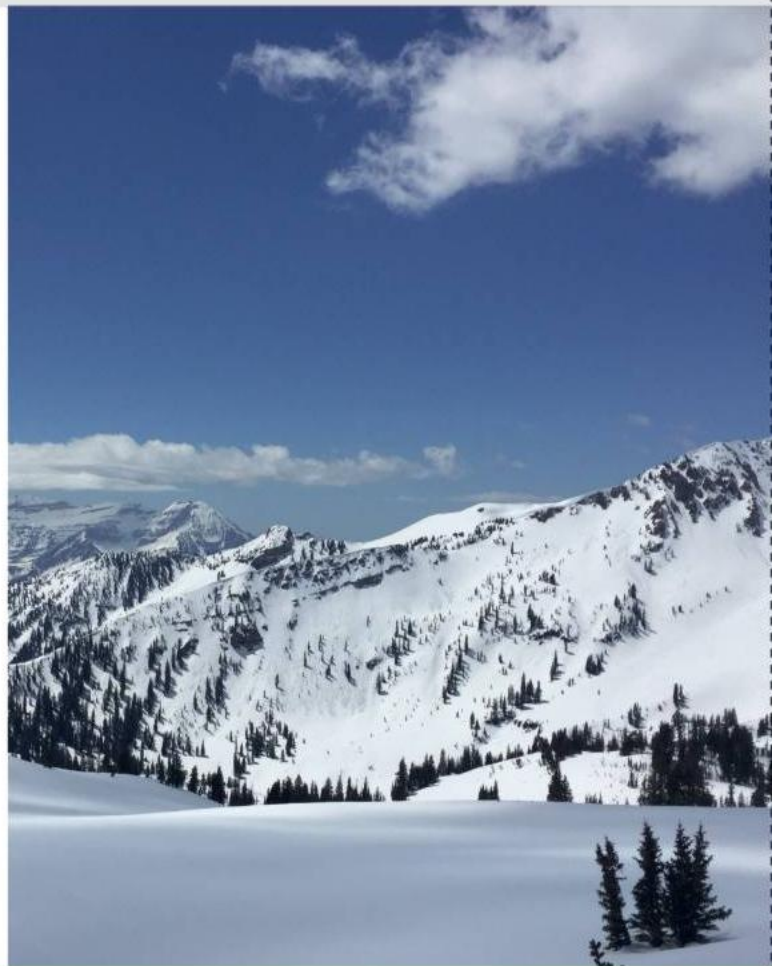
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gain in the logarithm is $(1 - 2) / 2 = -0.5$, which is negative. The game is multiplicative, so the expected gain in the logarithm of wealth is a better indicator of success than the expected gain in wealth itself.

All of the above stays true if the amount won by the poorer agent is 20 percent of the ante and the amount lost is greater than 16 ⅔ percent, just as Lysenko surmises. It will take the poorer agent longer to lose a given fraction of her initial wealth with those figures, but lose she inevitably and inexorably will. Only if the amount lost is less than 16 ⅔ percent does the game become favorable to her in the long run.

I hope these observations make it less counterintuitive to contemplate a dynamic in which most people are likely to lose in the end even though their expected gain in each coin flip is positive.

DRUG RACKET

“A Dilemma with New Drugs,” by Claudia Wallis [The Science of Health], brought back memories of my three decades of doing drug trials funded by both the National Institutes of Health and pharmaceutical companies. The article is correct in faulting our failure to accurately compare the effectiveness of new drugs with that of old ones. But the problem is much deeper. I stopped doing proprietary studies many years ago because it became clear that companies were not interested in finding better drugs but simply in putting out new ones under patent when the old patents expired. Advertising blitzes allow inferior and more expensive drugs to capture more than 80 percent of the market whether they are better or not.

Those ads are costly and certainly do not educate the consumer. Only two developed nations allow direct-to-consumer advertising of pharmaceuticals: the U.S. and New Zealand. And the U.S. is an outlier in expressly forbidding one of its federal programs—Medicare—from negotiating drug prices with manufacturers and in not regulating such prices overall. Consequently, we pay many times the price that other nations do. American pharmaceutical companies are much like an organized crime syndicate. Their campaign contributions to politicians have made our Congress guilty of aiding and abetting their crimes.

THOMAS M. VOGT *Portland, Ore.*

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BIG QUESTIONS FROM... **MIKE BROWN**

Astronomer Mike Brown is best known for driving demotion of Pluto to dwarf planet. Here, he discusses the next horizons in astronomy, at least in our solar system, what to look for when hunting for life on other worlds, and where we might find the elusive Planet 9.

Mike Brown killed Pluto. He had his reasons. But the astronomer did not set out to reclassify the solar system's ninth planet as a dwarf. Brown was interested in the Kuiper Belt, a region of icy comets and asteroids beyond Neptune's orbit. "I wanted to understand what was there," Brown says. "I thought there were probably new planets still to find."

Brown, a professor of planetary astronomy at the California Institute of Technology, was correct. Analyzing images from a nearby observatory, he and his team identified a number of new Kuiper Belt Objects.

Brown found these bodies by scouring a massive number of images taken by a telescope at a nearby observatory. When comparing images from different times, a planet's position will change from one exposure to the next. To identify objects that might be planets, Brown says, "I simply look for things that move."

One of the Kuiper Belt Objects he identified, Eris, is the most massive celestial body found in the solar system in more than a century. Since Eris was more massive than Pluto, astronomers soon began debating what it means to be a planet, a question that astronomers had considered long settled. Pluto lost, but science won.

"The Kuiper Belt has been in a deep freeze for the past four-and-a-half billion years," Brown says. "We are basically looking back to the earliest history of the

solar system."

Brown and Professors David Jewitt at University of California, Los Angeles, and Jane Luu at MIT Lincoln Laboratory, received the 2012 Kavli Prize in Astrophysics for their work.

Since then, Brown has discovered hundreds more Kuiper Belt Objects. "Every single time," Brown says, "there's this little charge of, 'Oh my God, this little ice ball at the edge of the solar system has never before been seen by human eyes until this very moment.' And that is always a moving experience."

Brown is still busy investigating the outer solar system, but he managed to tear himself away to discuss the next big mysteries in our corner of the universe, including why our solar system is such an oddball, whether it might harbor extraterrestrial life, and where we might finally find Planet 9.

What makes you think there's an undiscovered Planet 9?

In studying the little worlds in the Kuiper Belt, we realized that their orbits are not in a random jumble. Instead, they're all aligned—with orbits that are tilted compared to the solar system, and elongated, not circular like the orbits of other planets. When we first found this we spent a couple of years trying to convince ourselves that it was not caused by a planet. But we came to the conclusion that there's nothing else it could possibly be. This new planet is huge—probably six times more massive than Earth—so it gravitationally dominates this

vast region of space, forcing everything around it to march in line.

How will you find Planet 9?

We know it's probably 10 to 15 times farther away than Neptune; we know how it's tilted; and we basically know the path it travels through the sky. The one thing we don't know is where in that path it is. But I think we now know how to go through the universe of data that exists out there, and process it in a way that we can pick out Planet 9 moving across the sky, without necessarily having to go to any telescope at all. That's because all the planets in the solar system have been observed multiple times before they were officially discovered. So, you can look at images that have been taken and search for objects that are over here today, but maybe three months ago had been over there, and two years earlier had been somewhere else. Then you just have to figure out how to connect those three objects out of the billions of other things around them. Computationally, it's an incredibly intensive task, but it's one that I think we are now finally up to.

Why look?

To me, the search for Planet 9 is the continuation of what humans have done forever. Humans explore. The first humans, I'm sure, looked across the plains and wanted to know what was on the other side. Humans crossed oceans to find what was on the other side. The solar system is in a sense the biggest neighborhood that we have. So, by exploring it, we're making our neighborhood a little bit bigger. And once you admit the possibility of a Planet 9, and you think about how Planet 9

got there, there's no reason to not start asking the question about Planet 10, Planet 11, Planet 12. . . .

Why is our solar system so weird?

If you had asked 20 years ago if we understood the formation of the solar system, I think most astronomers would have said that we understand it pretty well. But in the last 25 years, we have repeatedly found planetary systems around other stars that are nothing like our solar system. We find giant planets parked in orbits closer than Mercury's orbit. We find stars with eight planets, small ones, inside Mercury's orbit. We find all of these crazy things that we would have never predicted could be possible. We seem so different from the typical planetary system that we see out there in the galaxy.

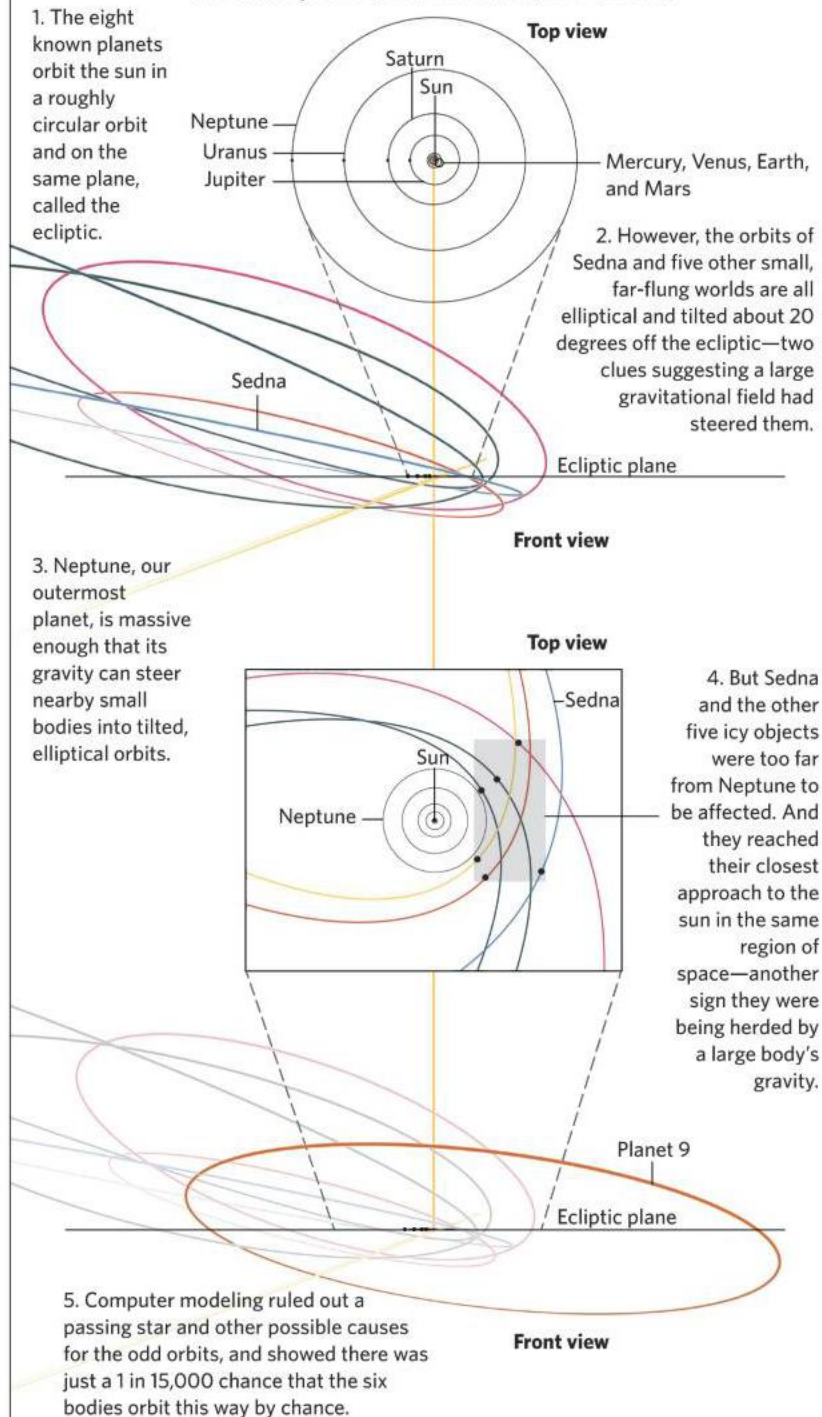
Do you think we'll ever encounter extraterrestrial life?

I think that the question about life elsewhere in our solar system is actually fascinating and answerable. If we could find life anywhere else in our solar system, it would be a sure-fire indicator that life is incredibly easy to start. If you have the right conditions, you have life. If we find microbial life in Europa, if we find life spewing out the vents on Enceladus, if we find hints of some sort of weird, methane-based life on Titan, then we would know that life is really easy to form—that we don't even need the conditions we think of as habitable. That would really tell us that life is pretty much everywhere.

To learn more, listen to a podcast with Mike Brown on ScientificAmerican.com. Also, stay tuned for the announcement of the next Kavli Prize laureates on May 27, 2020.

THE CASE FOR PLANET 9

Beyond Neptune in the Kuiper belt, millions of small icy bodies orbit the sun. The odd, far-flung orbits of six of them were clues to a distant, massive planet, one that could forever change how we see our solar system. (Orbital data courtesy of Mike Brown.)



THE  KAVLI PRIZE

Rough Weather from 5G Tech

Storm forecasts could lose reliability under new U.S. wireless standards

By the Editors

The rollout of 5G wireless technology will make mobile communications dramatically faster and more efficient. But 5G could also lead to dangerous setbacks for weather forecasting. That is the worry voiced by national and international science agencies and independent experts. The Federal Communications Commission (FCC), however, which regulates U.S. wireless networks, doesn't seem concerned—and that's a big problem.

5G promises better performance than earlier generations of wireless telecommunications. Some of 5G's frequency bands, however, are perilously close to those used by weather instruments on Earth-orbiting satellites. The 5G transmissions at 24 gigahertz can overlap with the 23.8-GHz signal naturally emitted by atmospheric water vapor and monitored by these instruments. Visible in day or night, through clear or cloudy skies, the 23.8-GHz signal is a reliable indicator of humidity that is used to sharpen weather forecasts—including the strengths, locations and paths of storms—on scales from hours to days. Unless, that is, the data are disrupted by some source of interference—such as the signals emitted by new 5G base stations and devices.

That interference is measured in units called decibel watts, and several agencies have called for relatively strict limits on how much of this electronic noise is permissible—the more negative the number, the stricter. The European Commission, for example, set a maximum threshold of -42 decibel watts. But during an inaugural auction last year for U.S. rights to use the 24-GHz transmission band, the FCC set a much looser noise limit of -20 decibel watts—well in excess of ceilings based on studies from NASA, the National Oceanic and Atmospheric Administration (NOAA), and the U.S. Navy. After the auction, NOAA acting administrator Neil Jacobs told Congress that the FCC's lax noise limits would result in as much as a 77 percent drop in satellite water-vapor data. This, Jacobs said, could lead to a two- to three-day lag in predicting the movements of hurricanes, effectively throwing the nation's satellite-based forecasting capabilities back to 1980 levels. Moreover, Jacobs testified, 5G interference could force NOAA to abandon plans for new weather satellites.

Yet late last fall delegates of the International Telecommunication Union Radiocommunication Sector (ITU-R), the organization managing global radio-spectrum use, agreed to introductory 5G noise limits of between -29 and -33 decibel watts. Taking effect this year, the ITU-R limits are more stringent than the FCC's but are still likely to be a problem for meteorologists.

Responding to congressional concerns before last spring's



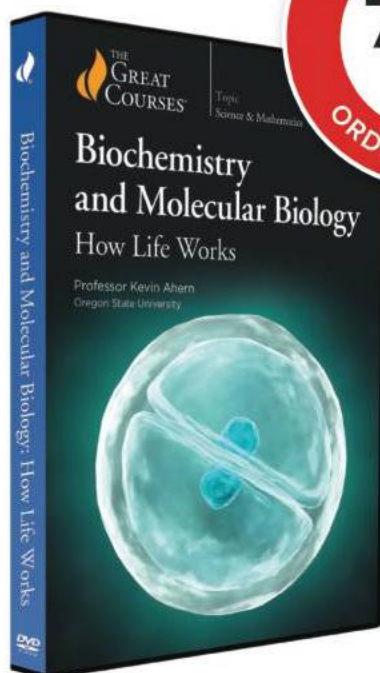
auction, commission chair Ajit Pai defended the decisions on 5G noise limits, calling criticisms “exaggerated and unverified last-minute assertions.” Yet it is the FCC, not its critics, that is failing to validate its claims: as of this writing, the commission has yet to produce any study supporting its recommended 5G noise limits. Meanwhile the agency is planning auctions of other 5G-frequency bands that overlap with satellite monitoring of precipitation, clouds and sea ice.

These actions are part of a broader, more disturbing pattern of imperious behavior by the FCC. The agency has already opened up previously protected regions of the radio spectrum for new uses while rapidly moving forward with approvals for globe-girdling constellations of satellites offering broadband Internet. Both types of activity could degrade a wide array of astronomical observations from ground-based telescopes, and a massive influx of new satellites also poses significant risks of creating more “space junk,” which already threatens existing orbital assets, including the International Space Station.

Fortunately, the FCC is not unaccountable. In a rare instance of congressional bipartisanship, in December 2019 the top Democrat and Republican on the House Science Committee jointly asked the Government Accountability Office to investigate why, exactly, the FCC's 5G recommendations differ so strongly from those of other federal agencies. This is a good start. Congress should use its considerable powers, budgetary and otherwise, to increase pressure on the FCC to “show its work” and to engage more meaningfully with dissenting government agencies, scientific institutions and other stakeholders to develop sustainable solutions for 5G—and for accurate weather forecasting. ■

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Biochemistry and its allied field of molecular biology are the fundamental sciences of life and the cornerstones of today's biotechnology revolution. But despite being about a subject that concerns us all—life—they are considered almost unapproachably difficult by non-scientists. Not anymore.

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What's Missing from Medical Training

Students need to understand how social factors determine health

By Erin Paquette and Angira Patel

Recently a former medical college official cautioned that the American College of Physicians “stepped out of its lane” by placing gun control in the purview of medical education. Stanley Goldfarb, formerly the associate dean of curriculum at the University of Pennsylvania’s Perelman School of Medicine, argued in the *Wall Street Journal* that teaching social justice issues and population health comes “at the expense of rigorous training in medical science” at a time when subspecialists are in short supply. But many physicians, ourselves included, think social issues should be at the heart of medical education.

Formal medical school typically takes four years, followed by several years of residency and often a fellowship, and during that short time students have a myriad of competing requirements. They must learn complex biological and chemical pathways that explain disease and health. They must be educated on how to read the scientific literature and apply it to their patients. They must master many therapies and know how to adapt them to patients’ varied disease states. On top of all this, they must learn to communicate effectively and compassionately with patients and colleagues.



Erin Paquette is an assistant professor of pediatrics and associate chair of the Lurie Children’s Ethics Advisory Board. **Angira Patel** is an associate professor of pediatrics and medical education and director of the McGaw Bioethics Clinical Scholars Program. Both are at Ann & Robert H. Lurie Children’s Hospital of Chicago.

Being a good doctor also demands that we understand the reasons behind poor health. Our mission is not simply to diagnose, manage and treat. Physicians should act to prevent the root causes of illness and improve well-being. The Centers for Disease Control and Prevention defines social determinants of health as “conditions in the places where people live, learn, work, and play” that affect their health outcomes and has as one of its Healthy People 2020 goals to “create social and physical environments that promote good health for all.” This goal serves our patients who are at risk for bad outcomes because they lack access to transportation or medications—or simply because of where they live.

Worldwide, life expectancy and health are directly linked with national spending on public health programs. The U.S., despite spending more on the treatment of individuals, ranks lower in life expectancy than nations that have similar overall health expenses but choose to direct funds to population-level interventions. Our own experiences underlie our perspective that teaching this is important. Practicing in Chicago, where people living only miles apart have different life expectancies—where black mothers disproportionately experience poor obstetrical outcomes and premature births as compared with their white counterparts, where residents name stress, drug abuse and depression as the greatest health threats to local children—we see the impact of social determinants of health on our patients. For individual patients, research tells us that high levels of toxic stress and adverse experiences create epigenetic changes that raise the risk of problems such as heart disease [see “The Health-Wealth Gap,” by Robert M. Sapolsky, *SCIENTIFIC AMERICAN*; November 2018].

We work daily to understand the best ways to teach medical students about social determinants of health. We offer classes on health equity and advocacy designed to place medicine in its larger social context. We lead bioethics curricula that guide students in making ethical decisions while incorporating principles of social justice, public health and population health. And we work with groups such as the National Collaborative for Education to Address the Social Determinants of Health, where the goal is to find and share best practices. It is through this kind of medical education and holistic understanding of systems that physicians begin to think about the total set of circumstances that brought the patient in front of us. As doctors, scientists and community members, what we want most is to prevent it from happening again.

Physicians are trained to tackle problems at their root. System- and structural-level social issues are also drivers of poor health, and it is our duty to address them. Rather than veering out of this lane, we should find ways to engage students here without sacrificing education in other areas. Medical training must evolve to produce doctors who are able to treat the individual but also understand the larger influencers of health—of which gun violence is most emphatically one. As medical professors, we would fail our students—and our patients—if we expected any less. ■

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ADVANCES



Laser light traveling through fiber-optic lines (*visualized here*) can provide ultra-detailed vibration measurements.

- White noise makes it easier to differentiate sounds
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- Bats find benefits in burned undergrowth
- Q&A: Ann Druyan imagines future worlds

SEISMOLOGY

Dark Fiber Detectors

Fiber-optic cables stretching below cities, above glaciers and along the seafloor could record earthquake vibrations and more

Celeste Labedz heard a sound like thunder roll across the ice. She was standing on Alaska's Taku Glacier, a vast field of snow-smothered ice between towering mountains, when the icequake began: a short-lived seismic tremor caused by the glacier's sudden movement. Immediately she scrambled for her notebook and jotted down the time. Labedz, a graduate student at the California Institute of Technology, would check that time against data from a fiber-optic cable she and her colleagues had just deployed to study such quakes—a promising new method that is shaking up geology and adjacent fields.

Information travels through a fiber-optic cable via pulses of laser light, most of which moves directly through the hair-thin glass threads. But inevitably a small amount hits microscopic flaws in the cable and scatters back toward the source. This reflection varies when the cable stretches or bends because of ground vibrations, such as those from an earthquake or even a passing truck, and scientists can monitor changes in the backscattered light to quantify those movements. First developed by the petroleum

GETTY IMAGES

industry a decade ago, this technique—known as distributed acoustic sensing (DAS)—has recently infiltrated the sciences. “The [DAS] community has just exploded in the past couple of years,” says Jonathan Ajo-Franklin, a geophysicist at Rice University. A workshop organized by the American Geophysical Union last December included scientists who had used the technique to image glaciers, monitor thunderstorms and peer into the deep ocean.

One major advantage to DAS is that fiber-optic cables can be many kilometers long, and a single one can act like a network of thousands of sensors covering every meter along its path. Conversely, conventional seismometers record ground motion only at a single point—a major roadblock to imaging the earth’s interior. When Mount St. Helens started rumbling ahead of its catastrophic 1980 eruption, for example, the fact that there was only one nearby seismometer meant that scientists could not tell if the quakes were actually caused by the awakening volcano. “Think of it like streetlights,” says Nathaniel Lindsey, a geophysicist now at Stanford University. “If you only have a few streetlights to illuminate the entire volcano, it’s not going to work that well.”

A second benefit is that fiber-optic cables already crisscross the world. Where-

as some sites, such as Taku Glacier, require new cables, others—locations from cities to the bottom of the sea—have unused cables or ones that can be adapted for DAS. Much of this availability stems from the dot-com boom of the 1990s, when telecommunications companies installed long stretches of cables; some of them, known as dark fiber, remain untapped. So scientists can simply connect one end to an “interrogator” unit, which fires a stream of laser pulses toward the other end and monitors any backscatter—and voilà, a new seismic wave-sensing network is ready to go.

Last year Tiejuan Zhu, a geophysicist at Pennsylvania State University, adapted unused cables in the college’s existing fiber network to search for subtle vibrations below campus. He was surprised to find multiple rumbles in his data on the night of a thunderstorm. Although scientists have long known that air vibrations from loud noises can rattle the earth’s surface, it was unclear whether the new technique could detect such “thunderquakes.” But when Zhu synchronized his results with data from NASA, there was no question. “I think there’s a big potential to ‘light up’ the urban area using this technology,” he says. “And not just to monitor earthquakes but also geohazards [such

as landslides or tsunamis] and weather.”

Other scientists are eyeing more remote targets. For a paper published last November in *Science*, Lindsey, Ajo-Franklin and Craig Dawe of the Monterey Bay Aquarium Research Institute attached an interrogator to a 20-kilometer fiber-optic cable typically used to transmit data from scientific instruments on the seabed off Monterey Bay. The system was down for maintenance, giving the scientists a chance to look for vibrations. In just four days they mapped multiple underwater fault zones and characterized seafloor trembling caused by waves above. More detailed seafloor maps will help scientists make better predictions about earthquakes and submarine volcanoes—both of which can cause life-threatening tsunamis.

Then there is the glacier work, for which Labedz and her colleagues have transformed a single cable into 3,000 seismic sensors. Early results show a five-hour stretch with 100 icequakes—many likely caused by meltwater forcing open crevasses within the glacier. Labedz’s academic adviser Zhongwen Zhan, a seismologist at Caltech, hopes to one day place permanent fiber-optic cables in Greenland or Antarctica to help researchers learn more about how glacier melt driven by climate change contributes to sea-level rise.

NEUROSCIENCE

A Helpful Hiss

White noise may help listeners distinguish between similar sounds

Scientists often test auditory processing in artificial, silent settings, but real life usually comes with a background of sounds like clacking keyboards, chattering voices and car horns. Recently researchers set out to study such processing in the presence of ambient sound—specifically the even, staticlike hiss of white noise.

Their result is counterintuitive, says Tania Rinaldi Barkat, a neuroscientist at the University of Basel: instead of impairing hearing, a background of white noise made it easier for mice to differentiate between similar tones. Barkat is senior author of the new study, published last November in *Cell Reports*.



It is easy to distinguish notes on opposite ends of a piano keyboard. But play two side by side, and even the sharpest ears might have trouble telling them apart. This is because of how the auditory pathway processes the simplest sounds, called pure frequency tones: neurons close together respond to similar tones, but each neuron responds better to one particular frequency. The degree to which a neuron

responds to a certain frequency is called its tuning curve.

The researchers found that playing white noise narrowed neurons’ frequency tuning curves in mouse brains. “In a simplified way, white noise background—played continuously and at a certain sound level—decreases the response of neurons to a tone played on top of that white noise,” Barkat says. And by reducing the number of neurons responding to the same frequency at the same time, the brain can better distinguish between similar sounds.

To determine whether the mice could differentiate between tones, the researchers used a behavioral test in which the rodents had to react to a specific frequency. Like humans, the mice easily recognized very different tones and struggled with similar ones. But with white noise added, the mice could better tell similar tones apart. The researchers investigated further

And Zhan has an even larger dream: to build the equivalent of a million-sensor array in California using about 1,000 kilometers of dark fiber. He has already converted 37 kilometers into a permanent seismic network below Pasadena and would like to do the same in other cities across the state. The data could reveal vulnerabilities in cities' infrastructure and could help alert citizens the instant an earthquake begins. "This is going to be a huge help in terms of preparing the community," Zhan says. At the moment, scientists cannot predict earthquakes—but a better understanding of the precursory shocks that occasionally lead up to a main quake could only help.

"Any more data about exactly how earthquakes start and nucleate could be a game changer," says Robert Mellors, a seismologist at Lawrence Livermore National Laboratory, who was not involved in the research.

But the quantity of data involved also presents a processing problem. DAS easily generates 10 terabytes a day for a single fiber-optic cable; that will add up to a petabyte in just 100 days. In comparison, the international seismological data repository—which collects all the seismological data available across the globe—contains less than a petabyte. Before scientists tap into dark fiber and deploy cables across remote areas, they will first have to learn how to store and share a colossal amount of information.

—Shannon Hall

by measuring neural activity in the mice's auditory cortexes as white noise played, and they also stimulated particular neurons directly to induce the curve-suppressing effect.

Future research should address how this mechanism works, says Kishore Kuchibhotla, a brain scientist at Johns Hopkins University, who was not involved in the study. And "the jury remains out on whether and how this relates to human perception," he adds.

It is possible that understanding this effect could eventually help people hear better. "Adding noise into the ear will not help someone with hearing loss," says Daniel Polley, who studies auditory neuroscience at Harvard University and also was not involved in the new study. "But learning how to turn down the hyperexcitability in the brain of someone with hearing loss could be helpful for hearing sounds in noise—as well as other related conditions, such as tinnitus and hyperacusis," hypersensitivity to loud sounds.

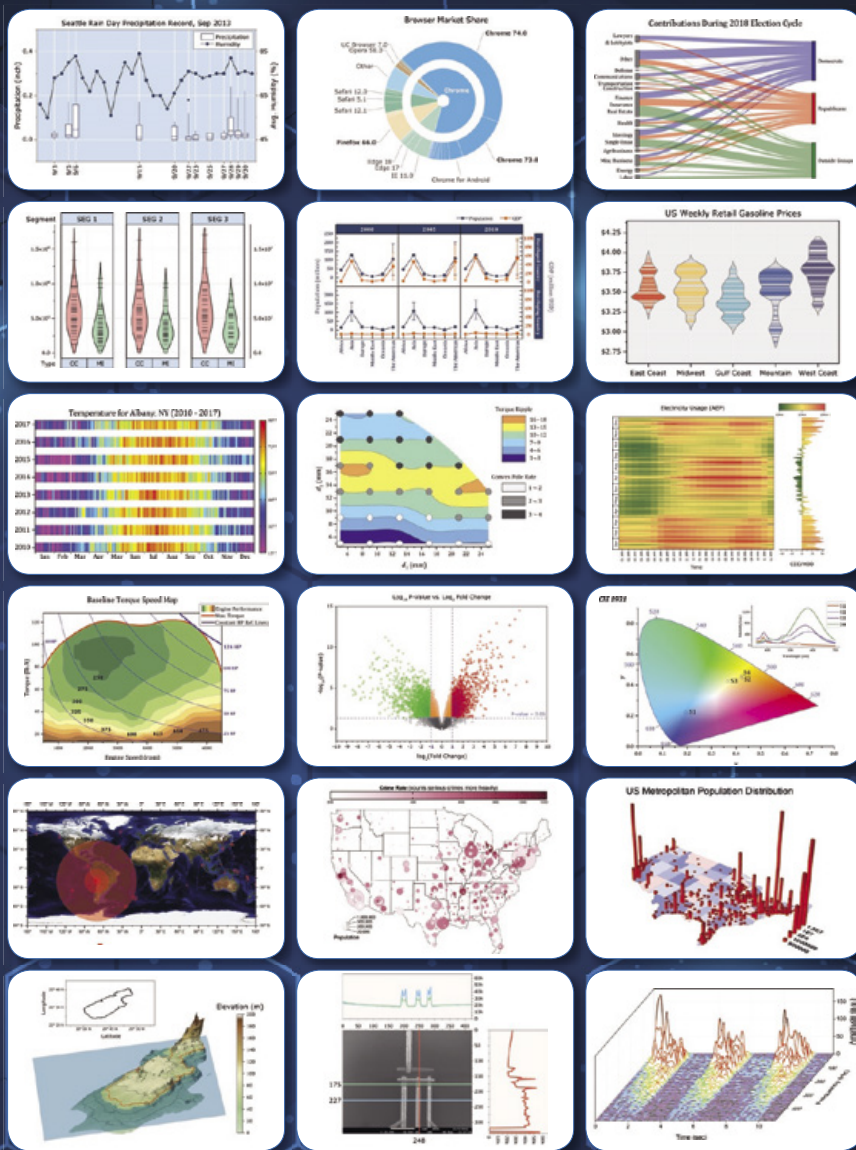
—Jillian Kramer



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BOTANY

Potato Signals

Sweet potato variety alerts neighbors to keep pests at bay

When nibbled, the leaves of one type of sweet potato release a strong-smelling chemical warning that prompts other leaves—on the same plant and those nearby—to produce defensive proteins that make them hard to digest. New research tracks this odorous alert system.

“It’s sort of a shortcut,” says Axel Mithöfer, a plant ecologist at the Max Planck Institute for Chemical Ecology in Jena, Germany, and co-author of the study, which appeared last November in *Scientific Reports*. Other plants have chemical warning systems that prompt neighbors to prepare for attack, but individual leaves often wait to manufacture defensive compounds until bitten themselves. But this plant’s leaves produce the compound immedi-



Sweet potato

ately when neighbors are bitten, he says.

To investigate this response, Mithöfer and his colleagues released caterpillars on the pest-resistant sweet potato strain Tainong (TN) 57 and its more susceptible cousin TN66, both native to Taiwan. Each “exhaled” at least 40 chemicals when attacked, but the TN57 leaves released twice the amount of a compound called DMNT, also found in other plant-defense responses.

Next, the scientists placed a healthy TN57 plant in a closed glass tank with one whose leaves had been pierced with tweezers. Within 24 hours high levels of a protein

called sporamin formed in both plants’ uninjured leaves. Sporamin, also found in sweet potato tubers themselves, is what makes it difficult for humans to digest them uncooked—and it causes trouble in insect guts, too. When researchers released synthesized DMNT into a tank with healthy plants, the leaves again readily formed sporamin.

Mithöfer’s team is now probing the mechanism TN57 leaves use to “smell” and “recognize” DMNT. The researchers also hope to test whether other chemicals the leaves release also elicit defenses.

Cesar Rodriguez-Saona, an entomologist at Rutgers University, who was not involved in the study, says this research showcases an intriguing defense mechanism—although he cautions that DMNT exposure in closed tanks could be higher than what plants experience in open, windy fields. It is also possible, he notes, that unattacked TN57s may not always expend the energy to use this direct defense “shortcut.” —Priyanka Runwal

PETER CHADWICK/Getty Images

MATERIALS SCIENCE

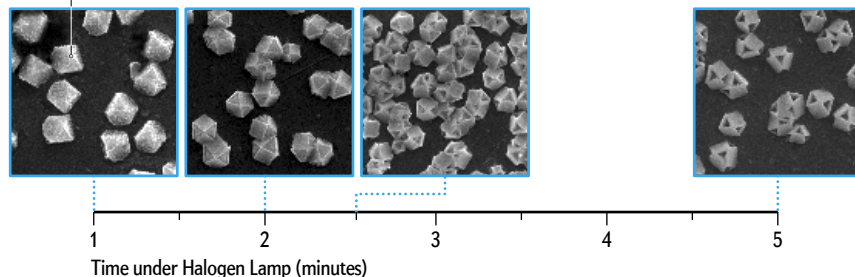
Sculpting with Light

A new process hollows tiny crystals to lead reactions such as carbon capture

For the first time, researchers have used light to control the shape of nanoparticles and create micron-size hollow shells from crystals of cuprous oxide (copper and oxygen). Such particles could have future applications as a low-cost catalyst to help pull excess carbon dioxide from the air, a way to improve microscopic imaging and more, says Bryce Sadtler, a chemist at Washington University in St. Louis and senior author of a study on the new method, published last October in *Chemistry of Materials*.

The hollowing process involves visible light, an alkaline solution and a source of voltage, Sadtler explains. Illuminating a cuprous oxide microcrystal excites its electrons, which join with copper ions to form regular copper atoms. No longer bound to oxygen, these atoms are free to jump to the particle’s surface and form a

Cuprous oxide microcrystal



copper metal coating that shields parts of the underlying crystal from the solution.

The crystal’s structure determines which of its faces are protected and which dissolve: Some faces’ atomic makeup lets electrons get excited more easily, bringing metal atoms to the surface. But the unprotected faces dissolve quickly, shaping the crystal along stark, geometric lines. “A diamond can only be [easily] cut a certain number of ways” for similar reasons, Sadtler says. Diamonds break most easily in line with rows of atoms in their crystal structure.

Stephen Maldonado, a chemist at the University of Michigan, who was not involved in the study, says the group’s findings “could be potentially useful in terms of designing catalysts for high-efficiency ...

CO₂ reduction, or something else.”

The large surface area and specific shape of the hollowed-out crystals could also be useful beyond facilitating a carbon-capture reaction, Sadtler says. In microscopic imaging, for example, existing methods are great for identifying solid, crystalline materials—but they struggle to identify biological molecules. According to Sadtler, similar hollowed structures could surround organic molecules, possibly in blood or urine samples, and boost the signal of the hard-to-detect matter. The researchers are also investigating different materials that strongly interact with light, such as iron and manganese oxides, which hold promise for hydrogen fuel-cell technology. —Leto Sapunar

CHU QIN



Antibiotics from cows may hinder plants' carbon fixing.

ECOLOGY

Manure Problems

Antibiotic use in cows alters carbon cycling

Since antibiotic drugs were first used in farm animals in the mid-1940s, a debate has raged about the prudence of this practice. A study published last December in *Ecology Letters* adds a new wrinkle: Farmers often use manure to build up soil carbon and increase nutrient availability for plants, but the study showed that dung from dairy cows given two types of routine antibiotics also altered the composition of soil bacteria and fungi. These shifts affected how plants “fixed” carbon dioxide from the atmosphere to convert into organic matter—a process that figures into strategies for climate change mitigation.

Carl Wepking, now at Colorado State University, led the experiments as a graduate student at Virginia Tech. Every month he hauled trash bags of cow manure to a grassy field and sprinkled 648 grams per square meter of three manure types onto three plots. Several months into the experiment, he covered the plots with Plexiglas chambers for seven days and pumped in carbon dioxide labeled with a specific carbon isotope for tracking. In the control plot, Wepking says, the manure from untreated cows had an overwhelmingly positive effect, boosting plant growth and retaining newly photosynthesized carbon in the plants and soil microorganisms. But

in the plots with manure from antibiotic-treated animals, more carbon was released again as carbon dioxide—roughly twice as much for one of the antibiotics. “Whether or not you give cows an antibiotic changes how carbon moves within the plants themselves,” he says, “which is wild.”

Soil stores about twice as much carbon as the atmosphere does, and increasing that storage could help address climate change. Francesca Cotrufo, a soil ecologist at Colorado State, who was not involved in the study, says climate and carbon-sequestration models increasingly account for the role plant compounds play in how efficiently microbes store carbon in the soil. Although the manure study does not account for carbon already stored, she adds, investigating antibiotics’ effects on more recently fixed carbon is a “novel and interesting angle” that “definitely should receive attention.”

Wepking suggests that because two different antibiotics (with different mechanisms of action) both reduced carbon-use efficiency, administering this category of drug to cows could potentially negate manure’s climate benefits. “What we’ve shown so far is that the positive effects of adding manure to the soil aren’t as positive as they looked, if your manure is coming from cattle that have been given antibiotics,” he says—although “it’s still kind of hard to tell” whether medicating livestock neutralizes or negates any net carbon-capture benefits of manure fertilizers. But it is critical to find out, he adds: U.S. livestock may contribute up to 13 million kilograms of antibiotics to the environment every year, and that figure is expected to increase. —Peter Andrey Smith

IN REASON WE TRUST



“It’s because I take God so seriously that I can’t bring myself to believe in him. In that way, it’s really a sign of respect.”

— Julia Sweeney

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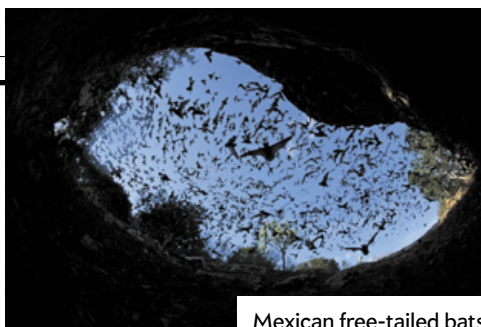
ANIMAL BEHAVIOR

Burn Benefits

Bat species proliferate in forests thinned by fire

Bats are nature's pest patrol. Every night the winged mammals venture forth from their caves and roosts to chow down on millions of insects, including some that plague farmers. But habitat loss and climate change, as well as infectious diseases such as white-nose syndrome, are hampering bats' ability to do their job. A new study adds another item to the list: wildfires. But not too many—too few.

In California's Sierra Nevada ecosystem, bats have adapted to occasional blazes. But a century of fire-suppression policies has kept some areas unburned for unusually long periods, resulting in denser forests with thicker undergrowth. "We wanted to see how these shifts in how fires are burning might be influencing bat biodi-



Mexican free-tailed bats

versity," says University of California, Berkeley, ecologist Zack Steel, who conducted the research while a graduate student at the University of California, Davis.

Steel and his colleagues deployed an array of microphones to count bats by recording their distinctive echolocation chirps and squeaks over four years at six sites in the Sierra Nevada. Three of the areas had recently endured fires, and three remained unburned.

Seventeen bat species call these forests home. The study revealed that eight of them tended to frequent the unburned patches, whereas 11 used the burned areas (some species visited both). "We expected to see one group of species benefiting from fire—the more open-habitat-adapted species—and another group, the more clutter-

adapted species, being negatively affected by fire, preferring the unburned areas," Steel says. "But even some of those species were occurring more often in burned areas."

What is ideal, the researchers write, is a combination of unburned areas and ones burned at different levels of severity—which they refer to as pyrodiversity. The results were published last December in the journal *Scientific Reports*.

"When there's lots of variation in habitat after a fire, many species benefit in different ways," says University of Connecticut biologist Andrew Stillman, who was not involved in the study. "On the whole, the community becomes more diverse, and that's a good thing for the landscape."

Extinguishing wildfires early leads to some species losing out on food and resources. "Fire is a natural part of the ecosystem, and many animals require the disturbance from fire to create the types of habitat that they need," Stillman adds. "It demonstrates another negative consequence of keeping wildfire away from fire-adapted forests in California." —Jason G. Goldman

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Mapping the Frozen Continent

A new view of Antarctica's bedrock could improve predictions about sea-level rise

Where and how fast will Antarctica lose ice as the climate warms, and how much will the sea level rise as a result? To answer these questions, scientists must learn as much as possible about the vast continent—despite the challenge of accurately surveying its topography underneath all that ice. The contours of Antarctica's bedrock help determine the behavior of glacial grounding lines, the zones where glacier ice transitions from resting on ground to floating on ocean water; if the line moves inland, a glacier loses more ice. Last December researchers published an upgraded bedrock map in *Nature Geoscience*, combining measurements from sources that

included airborne radar, satellite, seismic and snow accumulation data. The team estimated the topography for gaps between radar measurements using a more accurate, physics-based method, and they found striking differences from older maps—for instance, prior bedrock eleva-

tion estimates in some areas were up to 2,000 meters off.

The new map reveals good and bad news about potential ice loss in different parts of the continent. “There is not much hope for West Antarctica,” says Mathieu Morlighem, the study leader and an earth system scientist at the University of California, Irvine. “But East Antarctica is a mixed picture.” The study fills in crucial knowledge gaps about the continent's bedrock topography, says Jonathan Bamber, a glaciologist at the University of Bristol in England, who was not involved in the map project: “This is going to make our projections and simulations that much better for predicting sea-level rise.” —Annie Sneed

Previous Antarctica maps indicated that Recovery Glacier's underlying bedrock sloped upward going inland, which would make the glacier less vulnerable to grounding-line recession and increased ice loss. But the new map shows it actually slopes in the opposite direction, which means the glacier is more vulnerable and may foreshadow a faster recession of the grounding line. So far the glacier has been steady, but “this region is a major point of vulnerability in East Antarctica,” the study authors write.

Under the Ice

Elevation

–3,000 meters

4,200 m

Land below sea level (blue)

Land above sea level (brown)

Current ice extent (edge)

Current grounding line (black)
Boundary where ice goes from resting on bedrock to floating on water.

Thwaites is the fastest-changing Antarctic glacier, Morlighem says. Instead of discovering that the underlying bedrock has many ridges—which would help slow the glacier's loss of mass—researchers found only two, and they look unlikely to stop the recession of its grounding line and resulting ice loss.

Glaciers carry a significant portion of East Antarctica's ice through valleys in the Transantarctic Mountains and out onto the Ross Ice Shelf, so the bedrock topography here matters for that region. Thankfully, the researchers found a large ridge that runs below each glacier, which will help stabilize the area if the Ross Ice Shelf collapses.

The researchers made an astounding discovery underneath Denman Glacier: a vast canyon more than 3,500 meters below sea level, marking Earth's deepest point on land. Unfortunately, they also found

that the glacier's underlying bedrock slopes downward going inland, which makes this region “very vulnerable,” the study says. This kind of slope means the ice over the grounding line will be increasingly thick when the line recedes inland, leading to greater ice loss—and even more grounding-line recession. This region alone could contribute about 1.5 meters to sea-level rise.

50 kilometers

SCIENCE COMMUNICATION

Reimagining the Future

Cosmos co-creator Ann Druyan talks about communicating her dream for humanity

The universe in which the classic PBS series *Cosmos* debuted 40 years ago no longer really exists. In 1980 the Internet was in its infancy, scientists were just starting to sound the alarm about global warming, and present-day scientific realities such as exoplanets, dark energy and the Higgs boson remained entirely theoretical. Co-created by its host, the late astronomer Carl Sagan, with his wife Ann Druyan and their collaborator Steven Soter, the series' clear-eyed view of the past, present and future of life in the universe has been clouded over by the passage of time.

Today, however, Sagan's brainchild is in the midst of a modern reimagining that began in 2014 with Druyan as an executive producer, writer and director and with astrophysicist Neil deGrasse Tyson as host. This revival begins its third season, *Possible Worlds*, in March; an accompanying book by Druyan comes out in February. SCIENTIFIC AMERICAN spoke with her about *Cosmos*, science communication and her vision of a world made better and more beautiful through rational inquiry. —Lee Billings

What can we expect from this latest installment of *Cosmos*?

This new season contains a hopeful vision of the future and is a meditation on a remarkable quote from Einstein, from when he opened the 1939 New York World's Fair. I will paraphrase, but he was saying [that] science will not fulfill its mission the way art has until its inner meaning penetrates into the consciousness of the people. When I saw that quote, I recognized this was the original mission of *Cosmos*: to bring that inner meaning to everyone.

This season is in the shadow of climate change. I feel like I'm a member of a civilization that cannot awaken to the challenges that threaten to destroy it. One of the ways to awaken [people] is to give a dream of what the future could be if we use our science and technology with wisdom and fore-

sight and begin to think in the timescales of science. Not the next balance sheet, the next quarter, the next election, but 1,000 years from now. What will it be like?

What does it mean to use science that way?

For me, science is one of those rare occasions for human self-esteem, precisely because [science] is a kind of mechanism that says, "We're human, and we're going to deceive ourselves and each other. So let's create a system where no matter how much we may want to believe something, if it's not true, we'll come to know that over time." ... What happiness, what self-respect can we have unless we face reality and embrace it?

What "possible worlds" will *Cosmos* explore?

We go to lost worlds from our own history. Like the great city of Mohenjo Daro (in what is now Pakistan), which thousands of years ago had indoor plumbing and a glorious civilization—we bring that back to life. We go to the possible worlds on exoplanets, of course, but also to the planets of our own solar system.

We also explore inner worlds. For instance, we're fascinated by the concept of the "connectome" of the human brain—the idea that just as we've mapped the human genome, we could map all the thoughts, associations, memories and

ideas of a single human. Imagine putting that on an interstellar probe!

And we go to worlds right beneath our feet, looking more deeply at the ways other life-forms on this planet communicate. Like the democratic society of the bees, in which consensus arrives through waggle dancing. Here we are, thinking about messages from other extraterrestrial civilizations, when we are living in the midst of another society that communicates in symbolic language.

What is your dream for the future?

I have a theory that dreams are maps. And [today] we don't have a dream of a great future. I wanted to create a believable dream of the future [with] episode 13 of *Cosmos*, in which we go to the 1939 World's Fair, with its art deco sepia gorgeousness, and then to the 1964 World's Fair with its Kodachrome futuristic optimism, and then to the 2039 World's Fair. And what I'm most proud of is a new colossus in New York Harbor that consists of the carbon dioxide redeemed from the atmosphere that has been turned into calcium carbonate—limestone. Like a Statue of Liberty except it's the Tree of Life, with all the different species of biology.

That's my dream: that human ambition will be directed to making this planet, and the astonishing diversity of life that it supports, our priority. That's the possible world that ultimately all of *Cosmos* is driving to.



New York's 1964 World's Fair showed an optimistic view of progress.

IN THE NEWS

Quick Hits

By Sarah Lewin Frasier

GREENLAND

New simulations indicate that a rocky valley detected under the island's ice sheet may contain a 1,600-kilometer-long subterranean river, flowing from central Greenland to its northern coast.

ENGLAND

Researchers found 1,700-year-old chicken eggs, along with other ancient objects, in a waterlogged pit in southeastern England. A few eggs broke during extraction, releasing a sulfurous smell—but one remained intact, making it the only complete egg found from Roman Britain.

DOMINICAN REPUBLIC

A sunken museum at La Caleta Underwater National Park will preserve in place a ship that sank in 1725, complete with real (and replica) artifacts kept underwater for people to explore. Submerged artifacts often degrade faster when removed from the sea.

AUSTRALIA

To help boost Sydney Harbor's endangered seahorse population, scientists bred baby seahorses in an aquarium and built crab-trap-like undersea "hotels" to protect them as they adapt to the wild.

GREECE

Archaeologists uncovered gold, jewels and beads in a large building on the now uninhabited Minoan island of Chrysi, a location that about 3,500 years ago was devoted to making purple dye from sea snails called *Murex*.

ANTARCTICA

Scientists test-drove a meter-long, wheeled rover that streamed live views of the depths as it rolled along the underside of Antarctic ice. The Buoyant Rover for Under-Ice Exploration (BRUIE) could someday explore frozen-over seas on worlds such as Jupiter's moon Europa.

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Eclipse

That we need the sky
to tell us we don't matter
is why, before totality,
we are so giddy and akimbo.
In its random masking,
how shall the Sun disclose its other light?

(We've not seen before.) And strange

air, dark and gray and silver
and soft and very precise,
emerges to pool around every
pore and shiver of skin.

Beneath our breathy hollers,
a river runs dark, sprays of pebble
-leaping ripples instantly aloft: Corona
crowns the south: Hole edged
with brimming sprays of light!

What is metaphor but secular alchemy?

Black flat sphere five degrees off the ecliptic
else each month we'd see
totality, normal as a door,
common as a starling.

Above the Little Lost River,
above the valley and its ranges,
above thrall, dumb totality.

And the Moon slips away, unseen, three
millimeters monthly and so on
etcetera till its visage will shirk this scene.

Orbits bloat. Eclipses are happenstance. Like us,

they'll go extinct, the Moon to be
debris someday, a lovely
ring around a dead Earth.

But, ah, among the living: Crickets
at noon and humans hooting
with an owl, looking for

a gopher or at the light around the Moon:

Pink crust of flares like fire mountains,
like sleep to rub from the Cyclops's eye
before his hot day at the forge. There is

light around the Moon: White
corona, a hand of streaming cilia
that warns and beckons. The rim brightens,
and fact makes terror wonderful.

TEARS FROM A VOLCANO

Uniquely American stone ignites romance

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*"I love these pieces...
it just glowed...
so beautiful!"*

— S.S., Salem, OR



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enlarged
to show
luxurious
color

Stauer... *Afford the Extraordinary.®*



Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times*, *Time*, *Fortune* and the *New Republic*. She was science editor at *Time* and managing editor of *Scientific American Mind*.



Delirium: Taken Seriously at Last

The most common complication of surgery or hospitalization for older patients can often be prevented

By Claudia Wallis

As a young attending physician at a Connecticut medical center 35 years ago, Sharon Inouye was shocked by the disturbing changes she saw in many older patients. They would arrive at the hospital clear-headed and focused but soon became confused and disoriented—for no obvious or consistent reason. Some developed delusions and thrashing agitation; others seemed sedated and out of it. “I asked other physicians about it, and they were dismissive,” she recalls. This muddled state known as delirium “was taken as an expected thing” for older patients, but Inouye found it to be both unacceptable and deeply interesting. Now a geriatrician and professor at Harvard Medical School, she is one of the world’s leading investigators of delirium, the toll it can take and how to prevent it.

Delirium is astonishingly common. It affects between 10 and 50 percent of hospitalized patients aged 65 and older, whether they have had surgery or not, and up to 85 percent of those in intensive care units. It is the number-one complication of surgery in this demographic. And yet until recently, delirium was rarely

mentioned to patients or their families. One reason that is changing is the dramatic rise in elderly surgical patients. “It’s only in recent years that we started to see a large number of patients in their 80s and 90s coming to surgery,” says Frederick Sieber, chair of the department of anesthesiology and critical care medicine at Johns Hopkins University School of Medicine.

Another reason delirium is finally getting attention is that research by Inouye and others has shown that for many patients the condition is associated with longer-term risks, including loss of mental acuity. This is the phenomenon, sadly familiar to many families, of Grandpa never being quite the same after an operation. Whether delirium causes enduring harm to the brain or merely exposes and perhaps accelerates preexisting cognitive issues is not clear. Nor is it clear how anesthesia or surgery might trigger the condition. Sieber, for example, has extensively studied whether using local rather than general anesthesia and using mild versus heavy sedation make a difference. They do not. What seems to be driving the risk, he says, are underlying vulnerabilities that include chronic diseases and incipient dementia.

The consequences of delirium, if it lasts more than a few days and especially if it is followed by cognitive decline, are enormous. “It’s a house of cards,” Inouye says. “Patients start getting treated with medications for agitation or disruptive behavior, and those medications lead to complications. Or they are very sedated, and that leads to complications.” Delirious patients may choke on their food or pills and die of aspiration pneumonia. They may wind up in bed for long periods and suffer fatal blood clots. Once up, they are prone to falling. It’s a downward spiral and a costly one. Delirium adds more than \$183 billion a year to U.S. health care costs, outstripping congestive heart failure.

Fortunately, basic steps can be taken to prevent delirium or shorten its course, such as making sure the patient is well hydrated, has access to eyeglasses and hearing aids if he or she uses them, gets out of bed and walks as soon as possible, has adequate sleep, and is socially engaged by hospital staff and loved ones. These are some of the measures included in the [Hospital Elder Life Program](#) (HELP), first developed by Inouye and her colleagues in 1993 and now in use in hundreds of hospitals around the world. [Studies](#) show it reduces the risk of delirium by 30 to 50 percent, shortens its course when it does occur and cuts the rate of falls by 42 percent. Notably it saves between \$1,600 and \$3,800 per patient in hospital costs and more than \$16,000 in long-term care costs in the year following delirium.

This month AARP, via its affiliated Global Council on Brain Health, is releasing a report on delirium aimed at helping people reduce their risk and improve their outcome, particularly the 50 percent or so who will face surgery at some point after age 65, says Sarah Lenz Lock, senior vice president of policy and brain health at AARP. She wishes she had known more about it when her own mother “wiggled out” after an aortic repair. Lock says she would have set up bedside shifts with family so that her mom was never alone: “I would have made sure she went in hydrated and been prepared that recovery might take a little longer.” ■

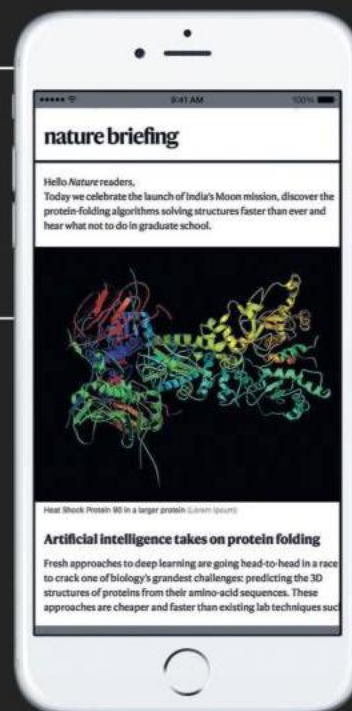
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Wade Roush is the host and producer of *Soonish*, a podcast about technology, culture, curiosity and the future. He is a co-founder of the podcast collective *Hub & Spoke* and a freelance reporter for print, online and radio outlets, such as *MIT Technology Review*, *Xconomy*, *WBUR* and *WHYY*.

Dollars for Dikes

Massive storm-surge barriers may be worth the cost

By Wade Roush

Ocean water expands as it soaks up heat from a warming atmosphere. Add in water from melting glaciers and ice sheets, and the global mean sea level will most likely rise by anywhere from 1.4 to 2.8 feet (43 to 84 centimeters) by 2100, according to the Intergovernmental Panel on Climate Change.

This gradual swelling will stress coastal cities, which are already seeing more sunny-day “nuisance flooding” at high tide. But the bigger threat is from waves and storm surges, which are amplified by higher sea levels. If greenhouse gas emissions go unchecked, by 2100 this combination will produce peak sea levels that are, on average, 1.9 to 5.6 feet higher than today’s mean sea level. As soon as 2050, the kind of extreme coastal flooding we currently expect every 100 years will occur *every year* at tropical latitudes and every 10 years in many U.S. coastal cities. By 2100 annual flood damage could amount to 9.3 percent of the global gross domestic product, or tens of trillions of dollars a year.

Most nations are not living up to their Paris Agreement com-

mitments to curb greenhouse gases, but even if they were, some sea-level rise would be inevitable. So there is really no choice but to try to defend our coasts.

The question is, How? Would it be smarter to build big, expensive surge barriers that protect entire harbors or to implement smaller-scale changes along the shoreline?

Not surprisingly, many city planners are attracted to the second, less costly option. In my hometown of Boston, which has a 47-mile shoreline, Mayor Marty Walsh’s “Resilient Boston Harbor” plan envisions a city buffered by restored marshes and by elevated parks, walkways and roads. Researchers at the University of Massachusetts Boston endorsed that approach in a 2018 preliminary study, concluding that such land-based resiliency measures would be more cost-effective than a barrier across the harbor’s mouth.

But the reality, I suspect, is that we will have to do both. Let’s say Boston elevated its frequently flooded Long Wharf and Seaport districts by three feet or so. That would fend off extra-high king tides, which occur when Earth, the moon and the sun align. But it would not help much against storm surges.

“Even though sea-level rise and storm surge are related, they are separate, distinct phenomena, and it’s important to address them with separate engineering and technology responses,” says William Golden, who filed the 1982 lawsuit that led to the cleanup of Boston Harbor and who later founded the National Institute for Coastal and Harbor Infrastructure, a Boston-based nonprofit. “What we feel is often possible and justifiable in urbanized areas is to focus on the concept of a layered defense: a land-based system on the perimeter to address sea-level rise integrated with a regional system of sea gates designed to prevent inundation from storm surge.”

The UMass researchers estimated the cost of Boston’s proposed Outer Harbor Barrier at \$8 billion to \$12 billion. Two huge “floating sector gates,” modeled on the mammoth Maeslantkering storm-surge barrier in the Netherlands, accounted for two thirds of that price tag. But there are cheaper options for sea gates, such as the \$550-million floating barge that would close off the “Ike Dike” proposed for Texas’s Galveston Harbor. And even at \$12 billion, a barrier might be a good investment. According to the U.K.’s Tyndall Center for Climate Change Research, a 100-year storm coming on top of a hypothetical 1.6-foot rise in sea level would threaten \$460 billion in assets in the Boston area alone.

At his nonprofit, Golden is working to gather Boston community leaders in a push for a more thorough study of the Outer Harbor Barrier that could help qualify the project for federal funding. “What we need now is to have an in-depth additional cost-benefit analysis, so that we make sure our public policy isn’t based on a preliminary study,” Golden says. “This is going to affect the city forever.” ■

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A detailed illustration of the cosmic web, showing a complex network of dark matter filaments and galaxy clusters. The filaments are depicted as glowing blue and purple lines, while the galaxy clusters are shown as dense regions of orange and yellow light. The overall structure is curved, suggesting the expansion of the universe.

COSMOLOGY

Two divergent measurements of how fast
the universe is expanding cannot both be right.
Something must give—but what?

A COSMIC CRISIS

By Richard Panek

Illustration by Mark Ross Studios

Richard Panek is the prizewinning author of *The 4% Universe* and the recipient of a Guggenheim Fellowship in Science Writing. His most recent book is *The Trouble with Gravity: Solving the Mystery Beneath Our Feet* (Houghton Mifflin Harcourt, 2019).



TOWARD THE END OF THE 20TH CENTURY, THE STANDARD COSMOLOGICAL MODEL seemed complete. Full of mysteries, yes. Brimming with fertile areas for further research, definitely. But on the whole it held together: the universe consisted of approximately two-thirds dark energy (a mysterious something that is accelerating the expansion of the universe), maybe a quarter dark matter (a mysterious something that determines the evolution of structure in the universe), and 4 or 5 percent “ordinary” matter (the stuff of us—and of planets, stars, galaxies and everything else we had always thought, until the past few decades, constituted the universe in its entirety). It added up.

Not so fast. Or, more accurately, too fast.

In recent years a discrepancy has emerged between two ways of measuring the rate of the universe’s expansion, a value called the Hubble constant (H_0). Measurements beginning in today’s universe and working backward to earlier and earlier stages have consistently revealed one value for H_0 . Measurements beginning at the earliest stages of the universe and working forward, however, have consistently predicted another value—one that suggests the universe is expanding faster than we had thought.

The discrepancy is mathematically subtle but—as subtle mathematical discrepancies magnified to the spacetime scale of the universe often are—cosmically significant. Knowing the current expansion rate of the universe helps cosmologists extrapolate backward in time to determine the age of the universe. It also allows them to extrapolate forward in time to figure out when, according to current theory, the space between galaxies will have grown so vast that the cosmos will look like an empty expanse beyond our own immediate surroundings. A correct value of H_0 might even help elucidate the nature of the dark energy driving the acceleration.

So far measurements of the early universe looking forward predict one value for H_0 , and measurements from the recent universe looking backward reveal another. This sort of situation is not rare in science. Usually it disappears under closer scrutiny—and the assumption that it would disappear has reassured cosmologists for the past decade. But the disagreement has, if anything, hardened year after year, each set of measurements growing more and more intractable. And now a consensus on the problem has emerged.

Nobody is suggesting that the entire standard cosmological model is wrong. But *something* is wrong—maybe with the observations or maybe with the interpretation of the observations, although each scenario is unlikely. This leaves one last option—equally unlikely but also less and less unthinkable: something is wrong with the cosmological model itself.

FOR MOST OF HUMAN HISTORY THE “STUDY” OF OUR COSMIC ORIGINS was a matter of myth—variations on the theme of “in the beginning.” In 1925 American astronomer Edwin Hubble edged it

IN BRIEF

Astronomers have repeatedly calculated the rate of the universe’s expansion—the Hubble constant—with two different techniques. These measurements have produced a seemingly intractable conflict.

One method, which involves measuring supernovae and stars in the relatively recent universe, arrives at one value. The other strategy, which uses light left over from shortly after the big bang, finds another.

Experimental problems could cause the discrepancy, but no one is sure what those problems would be. Another possibility is that the conflict points to undiscovered phenomena—“new physics.”

toward empiricism when he announced that he had solved a centuries-long mystery about the identity of smudges in the heavens—what astronomers called “nebulae.” Were nebulae gaseous formations that resided in the canopy of stars? If so, then maybe that canopy of stars, stretching as far as the most powerful telescopes could see, was the universe in its entirety. Or were nebulae “island universes” all their own? At least one nebula is, Hubble discovered: what we today call the Andromeda galaxy.

Furthermore, when Hubble looked at the light from other nebulae, he found that the wavelengths had stretched toward the red end of the visible spectrum, suggesting that each source was moving away from Earth. (The speed of light remains constant. What changes is the length between waves, and that length determines color.) In 1927 Belgian physicist and priest Georges Lemaître noticed a pattern: The more distant the galaxy, the greater its redshift. The farther away it was, the faster it receded. In 1929 Hubble independently reached the same conclusion: the universe is expanding.

Expanding from what? Reverse the outward expansion of the universe, and you eventually wind up at a starting point, a birth event of sorts. Almost immediately a few theorists suggested a kind of explosion of space and time, a phenomenon that later acquired the (initially derogatory) moniker “big bang.” The idea sounded fantastical, and for several decades, in the absence of empirical evidence, most astronomers could afford to ignore it. That changed in 1965, when two papers were published simultaneously in the *Astrophysical Journal*. The first, by four Princeton University physicists, predicted the current temperature of a universe that had emerged out of a primordial fireball. The second, by two Bell Labs astronomers, reported the measurement of that temperature.

The Bell Labs radio antenna recorded a layer of radiation from every direction in the sky—something that came to be known as the cosmic microwave background (CMB). The temperature the scientists derived from it of three degrees above absolute zero did not exactly match the Princeton collaboration’s prediction, but for a first try, it was close enough to quickly bring about a consensus on the big bang interpretation. In 1970 one-time Hubble protégé Allan R. Sandage published a highly influential essay in *Physics Today* that in effect established the new science’s research program for decades to come: “Cosmology: A Search for Two Numbers.” One number, Sandage said, was the current rate of the expansion of the universe—the Hubble constant. The second number was the rate at which that expansion was slowing down—the deceleration parameter.

SCIENTISTS SETTLED ON A VALUE FOR THE SECOND NUMBER FIRST. Beginning in the late 1980s, two teams of scientists set out to measure the deceleration by working with a common assumption and a common tool. The assumption was that in an expanding universe full of matter interacting gravitationally with all other matter—everything tugging on everything else—the expansion must be slowing. The tool was type Ia supernovae, exploding stars that astronomers believed could serve as standard candles—sources of light that do not vary from one example to another and whose brightness tells you its relative distance. (A

60-watt light bulb will appear dimmer and dimmer as you move farther away from it, but if you know it is a 60-watt bulb, you can deduce its separation from you.) If expansion is slowing, the astronomers assumed, at some great length away from Earth a supernova would be closer, and therefore brighter, than if the universe were growing at a constant rate.

What both teams independently discovered, however, was that the most distant supernovae were *dimmer* than expected and therefore farther away. In 1998 they announced their conclusion: The expansion of the universe is not slowing down. It is speeding up. The cause of this acceleration came to be known as “dark energy”—a name to be used as a placeholder until someone figures out what it actually is.

A value for Sandage’s first number—the Hubble constant—soon followed. For several decades the number had been a source of contention among astronomers. Sandage himself had claimed H_0 would be around 50 (the expansion rate expressed in kilometers per second per 3.26 million light-years), a value that would put the age of the universe at about 20 billion years. Other astronomers favored an H_0 near 100, or an age of roughly 10 billion years. The discrepancy was embarrassing: even a

Nobody is suggesting that the entire standard cosmological model is wrong. But something is wrong.

brand-new science should be able to constrain a fundamental number within a factor of two.

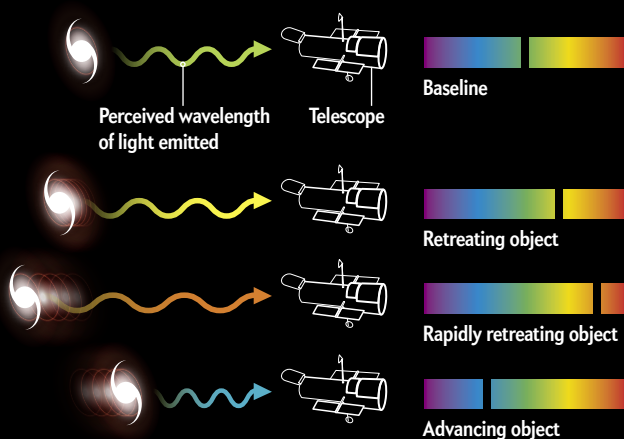
In 2001 the Hubble Space Telescope Key Project completed the first reliable measurement of the Hubble constant. In this case, the standard candles were Cepheid variables, stars that brighten and dim with a regularity that corresponds to their absolute luminosity (their 60-watt-ness, so to speak). The Key Project wound up essentially splitting the difference between the two earlier values: 72 ± 8 .

The next purely astronomical search for the constant was carried out by SH0ES (Supernovae, H_0 , for the Equation of State of Dark Energy), a team led by Adam G. Riess, who in 2011 shared the Nobel Prize in Physics for his role in the 1998 discovery of acceleration. This time the standard candles were both Cepheids and type Ia supernovae, and the latter included some of the most distant supernovae ever observed. The initial result, in 2005, was 73 ± 4 , nearly identical to the Key Project’s but with a narrower margin of error. Since then, SH0ES has provided regular updates, all of them falling within the same range of ever narrowing error. The most recent, in 2019, was 74.03 ± 1.42 .

All these determinations of H_0 involve the traditional approach of astronomy: starting in the here and now, the realm that cosmologists call the late universe, and peering farther and farther across space, which is to say (because the velocity of light is finite) further and further back in time, as far as they can see. In the past couple of decades, however, researchers have also begun using the opposite approach. They begin at a point as far away as they can see and work their way forward to the present. The cutoff point—the curtain between what we can

A Conflict at the Core of Cosmology

The value of the Hubble constant (H_0), which measures the universe's current rate of expansion, is both an essential and a controversial number for all of cosmology. In defiance of all expectations, estimates of H_0 from the "early" universe shortly after the big bang and from the "late" universe closer to the present day do not agree. The discrepancy may be the result of errors in either set of estimates, or it could reflect fundamental gaps in our current understanding of the universe.



CLOCKING SPEEDING GALAXIES

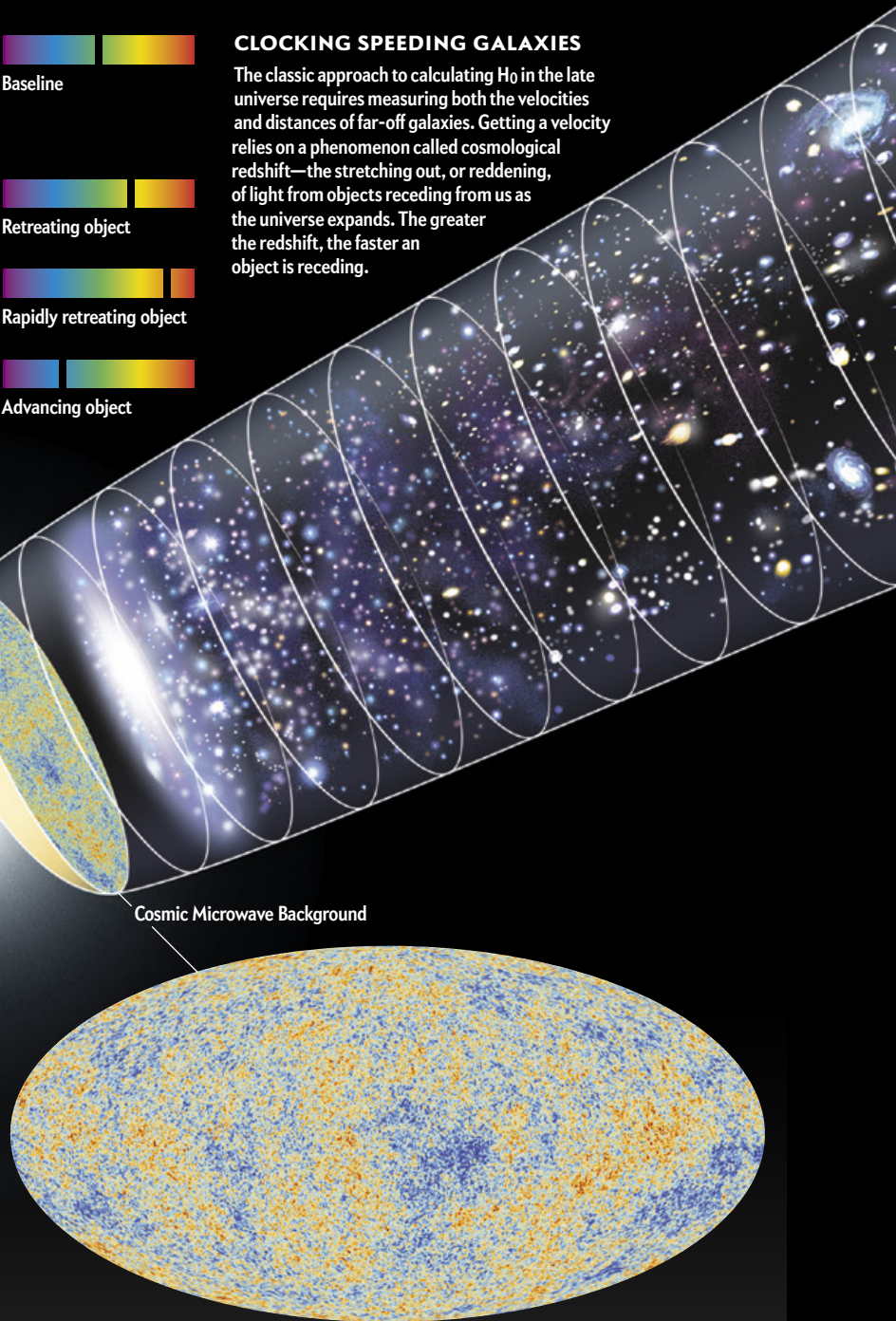
The classic approach to calculating H_0 in the late universe requires measuring both the velocities and distances of far-off galaxies. Getting a velocity relies on a phenomenon called cosmological redshift—the stretching out, or reddening, of light from objects receding from us as the universe expands. The greater the redshift, the faster an object is receding.

Big Bang

Cosmic Microwave Background

VIEW FROM THE EARLY UNIVERSE

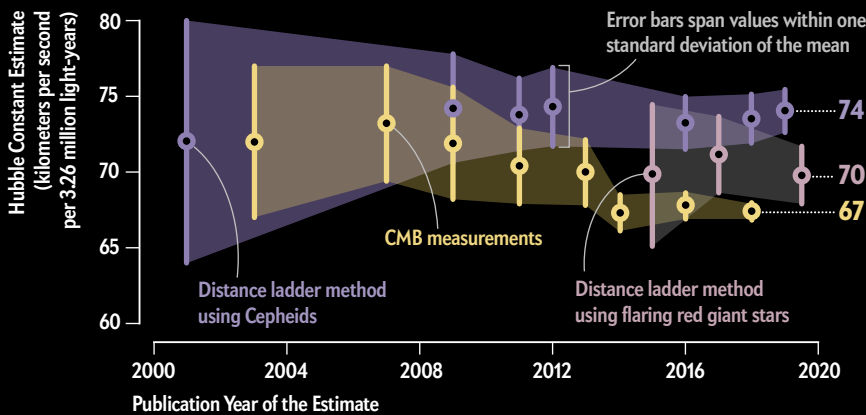
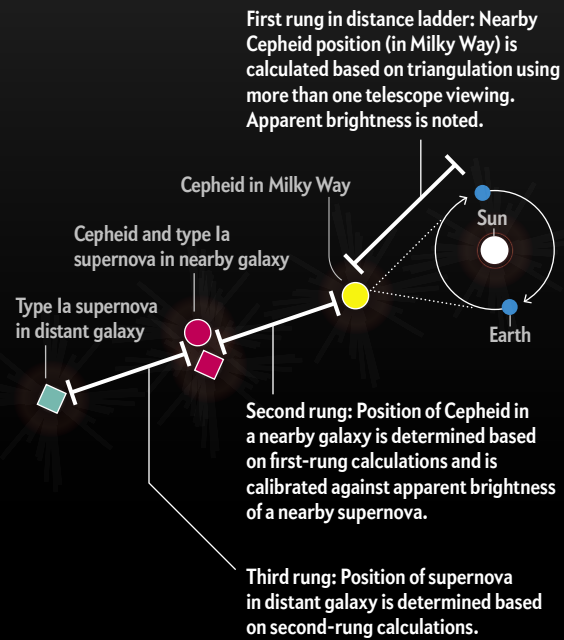
H_0 can also be measured using the cosmic microwave background (CMB), the big bang's all-sky afterglow from when the universe was just a 379,000-year-old expanse of dense, seething plasma. Sound waves reverberating through this plasma created overdensities and underdensities of matter that are imprinted on the CMB as minor temperature variations. By studying the size and other properties of these variations, cosmologists can use them as a "standard ruler" against which to chart the universe's subsequent growth and evolution. These studies, in turn, yield an estimate of H_0 .



Today

CLIMBING THE DISTANCE LADDER

Reckoning distances to remote galaxies is far harder than measuring their velocities via redshift. Astronomers seeking the late universe value of H_0 do this by ascending what is known as the cosmic distance ladder, in which different measurement methods are successively stacked to gauge vast distances. Cepheids—variable stars with known intrinsic brightness—typically constitute the ladder's first “rung” and can establish distances to nearby galaxies. More distant galaxies, however, require different, brighter objects with known intrinsic brightness—usually certain types of exploding stars called type Ia supernovae. Astronomers calibrate between these two distinct techniques using nearby galaxies harboring both Cepheids and type Ia supernovae.



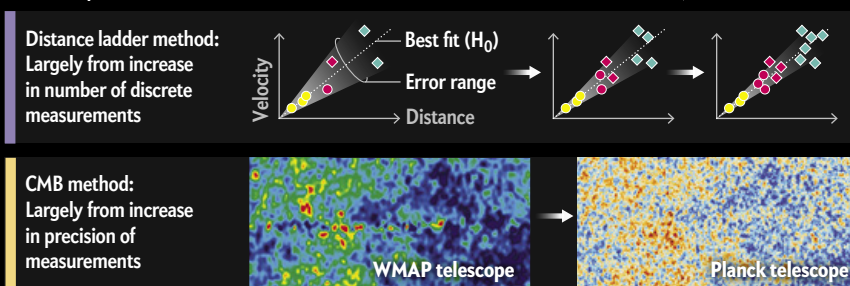
DIVERGING RESULTS

The CMB-based, early universe value for H_0 is 67 (in units of kilometers per second per 3.26 million light-years). The Cepheid-based, late universe value is 74. A new alternative to Cepheids—red giant stars that flare with a known intrinsic brightness—only complicated the tension. They indicated an H_0 of about 70—a value that is midway between the other two, with no overlap of error ranges.

TOWARD A MORE PERFECT UNION—OR NEW PHYSICS

Astronomers and cosmologists alike are working to increase the precision of their respective estimates of H_0 , progressively reducing uncertainties and possible errors in hopes their results may eventually overlap. Larger telescopes are gazing deeper into the cosmos, measuring Cepheids ever farther from Earth, and the CMB-mapping Planck satellite has dramatically improved on the measurements of its predecessor, the Wilkinson Microwave Anisotropy Probe (WMAP). If, however, the discrepancy endures, profound revisions to our cosmological models may be required.

Increased precision of Hubble constant calculations over time



ESA AND PLANCK COLLABORATION (Planck CMB); NASA AND WMAP SCIENCE TEAM (WMAP CMB detail); SOURCE: “THE CARNEGIE-CHICAGO HUBBLE PROGRAM, VII: AN INDEPENDENT DETERMINATION OF THE HUBBLE CONSTANT BASED ON THE TIP OF THE RED GIANT BRANCH,” BY WENDY L. FREEDMAN ET AL., IN *ASTROPHYSICAL JOURNAL*, VOL. 882, NO. 1, AUGUST 29, 2019 (diverging results chart)

and cannot see, between the “early” and the “late” universe—is the same CMB that the astronomers using the Bell Labs radio antenna first observed in the 1960s.

The CMB is relic radiation from the period when the universe, at the young age of 379,000 years old, had cooled enough for hydrogen atoms to form, dissipating the dense fog of free protons and electrons and making enough room for photons of light to travel through the universe. Although the first Bell Labs image of the CMB was a smooth expanse, theorists assumed that at a higher resolution, the background radiation would reveal variations in temperature representing the seeds of density that would evolve into the structure of the universe as we know it—galaxies, clusters of galaxies and superclusters of galaxies.

In 1992 the first space probe of the CMB, the Cosmic Background Explorer, found those signature variations; in 2003 a follow-up space probe, the Wilkinson Microwave Anisotropy Probe (WMAP), provided far higher resolution—high enough that physicists could identify the size of primitive sound waves made by primitive matter. As you might expect from sound waves that have been traveling at nearly the speed of light for 379,000 years, the “spots” in the CMB share a common radius of about 379,000 light-years. And because those spots grew into the universe we

If the source of the Hubble tension is not in the observations of either the late universe or the early universe, then cosmologists have little choice but to pursue option three: “new physics.”

study today, cosmologists can use that initial size as a “standard ruler” with which to measure the growth and expansion of the large-scale structure to the present day. Those measures, in turn, reveal the rate of the expansion—the Hubble constant.

The first measurement of H_0 from WMAP, in 2003, was 72 ± 5 . *Perfect*. The number exactly matched the Key Project’s result, with the additional benefit of a narrower error range. Further results from WMAP were slightly lower: 73 in 2007, 72 in 2009, 70 in 2011. No problem, though: the error for the SH0ES and WMAP measurements still overlapped in the 72-to-73 range.

By 2013, however, the two margins were barely kissing. The most recent result from SH0ES at that time showed a Hubble constant of 74 ± 2 , and WMAP’s final result showed a Hubble constant of 70 ± 2 . Even so, not to worry. The two methods could agree on 72. Surely one method’s results would begin to trend toward the other’s as methodology and technology improved—perhaps as soon as the first data were released from the Planck space observatory, the European Space Agency’s successor to WMAP.

That release came in 2014: 67.4 ± 1.4 . The error ranges no longer overlapped—not even close. And subsequent data released from Planck have proved just as unyielding as SH0ES’s. The

Planck value for the Hubble constant has stayed at 67, and the margin of error shrank to one and then, in 2018, a fraction of one.

“Tension” is the scientific term of art for such a situation, as in the title of a conference at the Kavli Institute for Theoretical Physics (KITP) in Santa Barbara, Calif., last summer: “Tensions between the Early and the Late Universe.” The first speaker was Riess, and at the end of his talk he turned to another Nobel laureate in the auditorium, David Gross, a particle physicist and a former director of KITP, and asked him what he thought: Do we have a “tension,” or do we have a “problem”?

Gross cautioned that such distinctions are “arbitrary.” Then he said, “But yeah, I think you could call it a problem.” Twenty minutes later, at the close of the Q and A, he amended his assessment. In particle physics, he said, “we wouldn’t call it a tension or a problem but rather a crisis.”

“Okay,” Riess said, wrapping up the discussion. “Then we’re in crisis, everybody.”

UNLIKE A TENSION, WHICH REQUIRES A RESOLUTION, OR A PROBLEM, which requires a solution, a crisis requires something more—a wholesale rethink. But of what? The investigators of the Hubble constant see three possibilities.

One is that something is wrong in the research into the late universe. A cosmic “distance ladder” stretching farther and farther across the universe is only as sturdy as its rungs—the standard candles. As in any scientific observation, systematic errors are part of the equation.

This possibility roiled the KITP conference. A group led by Wendy L. Freedman, an astrophysicist now at the University of Chicago who had been a principal investigator on the Key Project, dropped a paper in the middle of the conference that announced a contrarian result.

By using yet another kind of standard candle—stars called red giants that, on the verge of extinction, undergo a “helium flash” that reliably indicates their luminosity—Freedman and her colleagues had arrived at a value that, as their paper said, “sits midway in the range defined by the current Hubble tension”: 69.8 ± 0.8 —a result that offers no reassuring margin-of-error overlap with that from either SH0ES or Planck.

The timing of the paper seemed provocative to at least some of the other late universe researchers in attendance. The SH0ES team in particular had little opportunity to digest the data (which the scientists tried to do over dinner that evening), let alone figure out how to respond.

A mere three weeks later, though, they posted a response paper. The method that Freedman’s team used “is a promising standard candle for measuring extragalactic distances,” the authors began, diplomatically, before eviscerating the systematic errors they believed affected the team’s results. Riess and his colleagues’ preferred interpretation of the red giant data restored the Hubble constant to a value well within its previous confines: 72.4 ± 1.9 .

Freedman vehemently disagrees with that interpretation: “It’s wrong! It’s completely wrong!” she says. “They have misunderstood the method, although we have explained it to them at several meetings.”

(In early October 2019, at yet another “tension” meeting, the dispute took a personal turn when Barry Madore—one of Freedman’s collaborators, as well as her spouse—showed a slide that depicted Riess’s head in a guillotine. The image was part of a science-related chopping-block metaphor, and Madore later said that including Riess’s head was a joke. But Riess was in the audience; suffice to say that the next coffee break included, at the insistence of many of the attendees, a discussion about professional codes of conduct.)

Such squabbles cannot help but leave particle physicists figuring that, yes, the problem lies with the astronomers and the errors involving the distance ladder method. But CMB observations and the cosmic ruler must come with their own potential for systematic errors, right? In principle, yes. But few (if any) astronomers think the problem lies with the Planck observatory, which physicists believe to have reached the precision threshold for space observations of the CMB. In other words, Planck’s measurements of the CMB are probably as good as they are ever going to get. “The data are spectacular,” says Nicholas Suntzeff, a Texas A&M astronomer who has collaborated with both Freedman and Riess, though not on the Hubble constant. “And independent observations” of the CMB—at the South Pole Telescope and the Atacama Large Millimeter Array—“show there are no errors.”

If the source of the Hubble tension is not in the observations of either the late universe or the early universe, then cosmologists have little choice but to pursue option three: “new physics.”

FOR NEARLY A CENTURY NOW SCIENTISTS HAVE BEEN TALKING ABOUT new physics—forces or phenomena that would fall outside our current knowledge of the universe. A decade after Albert Einstein introduced his general theory of relativity in 1915, the advent of quantum mechanics compromised its completeness. The universe of the very large (the one operating according to the rules of general relativity) proved to be mathematically incompatible with the universe of the very small (the one operating according to the rules of quantum mechanics).

For a while physicists could disregard the problem, as the two realms did not intersect on a practical level. But then came the discovery of the CMB, validating the idea that the universe of the very large actually emerged from the universe of the very small—that the large-scale galaxies and clusters we study with the help of general relativity grew out of quantum fluctuations. The Hubble tension arises directly out of an attempt to match those two types of physics. The quantum fluctuations in the CMB predict that the universe will mature with one value of the Hubble constant, whereas the general relativistic observations being made today are revealing another value.

Riess likens the discrepancy to a person’s growth. “You’ve got a child, and you can measure their height very precisely when they’re two years old,” he says. “And you can then use your understanding of how people grow, like a growth chart, to predict their final height at the end.” Ideally the prediction and measurement would agree. “In this case,” he says, “they don’t.” Then again, he adds, “We don’t have a growth chart for how universes usually grow.”

And so cosmologists have begun entertaining the radical—yet not altogether unpalatable—possibility that the standard cosmological model is not as complete as they have assumed it to be.

One possible factor affecting our understanding of the universe’s growth is an uncertainty about the particle census of the universe. Most scientists today are old enough to remember another imbalance between observation and theory: the “solar neutrino problem,” a decades-long dispute about electron neutrinos from the sun. Theorists predicted one amount; neutrino detectors indicated another. Physicists suspected systematic errors in the observations. Astronomers questioned the completeness of the theory. As with the Hubble constant tension, neither side budged—until the end of the millennium, when researchers discovered that neutrinos, unexpectedly, have mass; theorists adjusted the Standard Model of particle physics accordingly. A similar adjustment now—for instance, a new variety of neutrino in the early universe—might alter the distribution of mass and energy just enough to account for the differences in measurement.

Another possible explanation is that the influence of dark energy changes over time—a reasonable alternative, considering that cosmologists do not know how dark energy works, let alone what it is.

“There is a small correction somewhere needed to bring the numbers into agreement,” Suntzeff says. “That is new physics, and that is what excites cosmologists—a kink in the wall of the Standard Model, something new to work on.”

Everybody knows what they have to do next. Observers will await data from Gaia, a European Space Agency observatory that promises, in the next couple of years, unprecedented precision in the measurement of distances to more than a billion stars in our galaxy. If those measurements do not match the values that astronomers have been using as the first rung in the distance ladder, then maybe the problem will have been systematic errors after all. Theorists, meanwhile, will continue to churn out alternative interpretations of the universe. So far, though, they have not found one that withstands community scrutiny. And there, barring any breakthrough, the tension—problem, crisis—will have to reside for now: in a quasi-unscientific universe harboring a predicted Hubble constant of 67 that belies the observation of 74.

The standard cosmological model remains one of the great scientific triumphs of the age. In half a century cosmology has matured from speculation to (near) certainty. It might not be as complete as cosmologists believed it to be even a year ago, yet it remains a textbook example of how science works at its best: it raises questions, it provides answers and it hints at mystery. ■

MORE TO EXPLORE

Planck 2018 Results. VI. Cosmological Parameters. Planck Collaboration.

Preprint posted July 17, 2018, to <https://arxiv.org/abs/1807.06209>

Large Magellanic Cloud Cepheid Standards Provide a 1% Foundation for the Determination of the Hubble Constant and Stronger Evidence for Physics Beyond Λ CDM. Adam G. Riess et al. Preprint posted March 18, 2019, to <https://arxiv.org/abs/1903.07603>

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FROM OUR ARCHIVES

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scientificamerican.com/magazine/sa

THE HIDDEN TOLL OF WILDFIRE

A photograph taken from the cockpit of a NASA DC-8 aircraft, looking out over a massive wildfire plume. The plume is a thick, white and grey cloud of smoke and ash that rises high into the sky, partially obscuring the blue sky. The aircraft's wing and part of the cockpit structure are visible in the foreground, framing the view of the fire.

CHEMISTRY

AS BLAZES WORSEN
GLOBALLY, AN
AERIAL CAMPAIGN
SEEKS TO
UNDERSTAND HOW
EMISSIONS AFFECT
HUMAN HEALTH

By Kyle Dickman

Photographs by Matt Nager

FROM THE COCKPIT of NASA's DC-8, a pilot views the Ridgetop Fire in Montana. Onboard, scientists and engineers collect data on emissions as they fly through and downwind of the plume.



Kyle Dickman is a freelance journalist and a contributing editor at *Outside* magazine. He is author of *On the Burning Edge* (Ballantine Books, 2015). He spent five seasons fighting wildfires in California.



“THIS IS INTERESTING. NOT TOO THICK,” SAID Jim Crawford, an atmospheric chemist wearing a motion-sickness patch behind his ear. It was afternoon in late July 2019, and Crawford was bearing down on a skein of wildfire smoke visible from the cockpit of a former commercial jet that NASA had retrofitted into an airborne laboratory. In the cabin, 35 scientists and engineers were calibrating their instruments. The mood was wired: Would their tools, most designed to measure urban pollutants, work in air thick with particulates? How would the 50-year-old plane respond in a smoke column? The DC-8 shuddered and jumped as it entered a plume lofted 12,000 feet high by a fire outside of Missoula, Mont. “Forty-five seconds, then turn it around,” Crawford directed the pilots. The turbulence was surprisingly mild, and he wanted to go back through it.



This was only the third flight in the aerial segment of FIREX-AQ, an ambitious three-year project led by the National Oceanic and Atmospheric Administration and NASA. It is attempting to sniff out the precise chemical composition of smoke emitted from biomass burns and determine, among other things, when, and why, it is most dangerous for human health. For six weeks last summer the DC-8 and a pair of Twin Otters similarly quilled with atmospheric-sampling instruments flew through more than 100 different columns. They ranged from a bubble of smoke rising off a tiny agricultural burn in Kansas to a mushroom cloud that shot up 31,000 feet from the Williams Flats Fire in Washington State, a burn one scientist compared to a volcanic eruption. Never before has biomass smoke been studied in such detail and range. Although fires contribute up to a third of all particles in the atmosphere, “there are very few studies that examine the spe-

cific role of the different components of smoke on disease and the severity of the disease when people are exposed,” said a director at the Environmental Protection Agency in 2018.

We know that chronic exposure to fine particulate matter, which is in all smoke, can lead to heart and lung disease, irregular heartbeats and aggravated asthma, among other issues. It was estimated to cause 4.2 million premature deaths worldwide in 2016. Likewise, long-term exposure to ozone, a gas that can form via chemical reactions when smoke enters the atmosphere, is blamed for at least one million premature deaths a year. What we lack is a fundamental understanding of how and when these toxic components and others form in different types of biomass smoke. Currently air-quality regulators treat emissions from all biomass burns as the same, even though that is not the case. By learning about these processes, the FIREX-AQ team hopes to

IN BRIEF

The acute and chronic effects of wildfire smoke exposure in humans is poorly understood. As wildfires intensify and occur in new places, they are a growing public health threat.

An unprecedented project led by NOAA and NASA amassed more than 400 scientists to investigate the precise chemical composition of smoke emitted from biomass burns and how it changes over time.

Data collected during the aerial campaign will help determine what kinds of fires are most harmful. This could inform how fire management, such as lighting prescribed burns, is regulated and practiced.



LICK CREEK FIRE in Idaho is one of the Western wildfires FIREX-AQ chose to investigate on August 2, 2019.

improve the accuracy of wildfire-emissions forecasts, so that coaches know better when to cancel soccer practice, hospitals can anticipate an influx of immunocompromised people and regulators can protect outdoor workers from dangerous exposure. Their data could also help land managers light controlled burns, which mitigate the severity and health impacts of future wildfires.

Crawford checked his tablet, scrolling through real-time updates of the hundreds of particles and gases being sampled. The last time he had flown in the DC-8 was to study urban pollutants in Seoul, South Korea. Even in small cities, he said, researchers see pollution that is much worse than what he and his team were witnessing that day. “But how do all these fires add up?” he asked. “How much ozone do fires produce? What’s the chemistry for how it forms? And how do you regulate a natural phenomenon?” Carsten Warneke, a fellow principal investigator of FIREX-AQ, who is based out of NOAA’s Earth Systems Research Laboratory in Boulder, Colo., explains that air-quality models treat wildfire smoke as a smog event when it is a completely different problem.

Some 350 miles to the south, on the Gowen Field Air National Guard Base in Boise, Idaho, Warneke and 50 more scientists were sifting through meteorological patterns, fuels, real-time satellite data and ongoing fire updates to determine which of the West’s wildfires met the most criteria for FIREX-AQ’s goals. “There are a

lot of scientists, and they all want slightly different things,” said Amber Soja, an associate research fellow at the National Institute of Aerospace, who was responsible for briefing the 400 researchers involved in FIREX-AQ on that day’s fire activity.

For today’s mission, the team had picked the North Hills Fire in Montana as the DC-8 taxied onto the runway for takeoff. It had the most pronounced smoke column of the nine fires being considered. At a relatively small 4,600 acres, the blaze was wholly unremarkable—and that is what made it scientifically alluring. Although U.S. Forest Service firefighters were still working to control the flames, they granted the DC-8 permission to sample the plume at different points in time and space, thereby capturing what was in the smoke and how it changed as it moved downwind, interacting with new conditions and environments.

After passing through the plume for the 16th time in an hour, Crawford received a message from Warneke at mission command. It contained a satellite image of a smoke column shooting above the clouds just below California’s Mount Shasta, almost 800 miles to the southwest. Warneke had drawn a circle around the plume and scrawled next to it in red ink, “GO HERE NOW!”

AN UNPRECEDENTED PROJECT

FIREX-AQ, or Fire Influence on Regional to Global Environments and Air Quality, was born in Montana’s Fire Lab. There NOAA research chemist Jim Roberts, who was part of the team that developed a technique for measuring atmospheric nitrogen during the ozone crisis of the 1970s, had grown interested in investigating the acids present in wildfire smoke. In 2009, while burning ponderosa pine branches and other fuel characteristic of the Western U.S., he found a particularly noxious compound called isocyanic acid. Regular exposure in humans, from sources such as cigarettes and cooking fires, can cause cataracts, rheumatoid arthritis and heart disease. Soon after, Roberts was in his office in Boulder, Colo., when the most destructive wildfire in the state’s history broke out, burning tens of thousands of acres and destroying several hundred homes on the town’s outskirts.

Curious about whether his lab findings would hold up in the real world, Roberts dragged out an instrument that measures acids to test Boulder’s air. He found the highest concentration of isocyanic acid ever measured in the atmosphere. Before that, no one had thought to look for it. “I didn’t sleep for two nights,” he says. “The biomass-burning community was completely unaware isocyanic acid was in smoke. What else didn’t we know?”

Generally speaking, air quality in U.S. cities has improved greatly since Congress passed the Clean Air Act in 1970. But when wildfires burn near urban areas, smoke undoes those gains. In 2019 the top eight most polluted cities in America by measure of ozone were all in the West. By measure of PM 2.5—particulate matter smaller than 2.5 microns that can embed in human lungs and enter the bloodstream—23 of the top 25 cities were in the West or Alaska. That trend is all but certain to hold: the Forest Service now anticipates a doubling of annual acreage burned by 2050.

Chief among the culprits for this problem is climate change: the West is becoming warmer and drier. In July 2019 climate modeler Park Williams of Columbia University published findings in the journal *Earth’s Future* showing that California’s fivefold increase in acreage burned between 1972 and 2018 was very likely linked to a 1.4-degree Celsius increase in hot-day temperatures. Anthropogenic warming, he says, is to blame.



Forest conditions also play a significant role in worsening fires. After 100 years of aggressive suppression of fires that were essential for Western ecosystems, the density in many forests now exceeds their historic norms. For example, in some parts of California's Sierras there are 1,000 trees per acre where there were once between 50 and 70. Meanwhile humans keep moving into fire-adapted biomes. In the 1990s 30.8 million people in the U.S. lived next to or on lands that regularly burned; 43.4 million do two decades later. The deadly convergence of these trends was on full display in 2018's Camp Fire, a blaze that razed the 26,800-person town of Paradise, Calif., burning 18,804 buildings and killing at least 85 people, most before the sun had fully risen.

About 4 percent of the entire globe burns every year, and increasing destructiveness is hardly an American problem alone. At the time of this writing, Australian bushfires that broke out at the end of 2019 had burned more than twice the area of California's 2018 fires and the Amazon's 2019 fires combined. Although the total acreage that burns annually is shrinking as natural places are converted into ranches and cropland, climate change is now fostering blazes in environments that have no historical record of raging burns while intensifying fires in places that do. In the summer of 2018 Northern Ireland saw unprecedented big fires. So did 7.4 million acres in Arctic and sub-Arctic Siberia. Fire scientist Stephen Pyne, a professor emeritus at Arizona State University, has dubbed this era the Pyrocene.

NOAA scientists did not come to wildfire smoke directly; ignoring it just became impossible. In the early 2000s, while studying haze transported to the Alaskan Arctic via Asia, as well as air

quality outside of Northeastern cities, they were surprised to see the chemical footprints of wildfires stamped all over their data. "We'd been focused on urban pollution over the years, but we'd fly through these urban areas and see all this stuff from wildfires," Roberts says. He grew convinced that smoke and air quality deserved the full weight of NOAA's research focus. Then, as now, observational forecasts of fire emissions were unreliable. In a 2008 article in the *Journal of Applied Remote Sensing*, a comparison of four fire-emissions models found that estimates of monthly contributions to atmospheric carbon could be off by a factor of 10. One problem was that North American fire-emissions models were based on data collected from just 39 different fire events—a paucity of data considering the variability in fires.

Their interest piqued, Roberts and Warneke, research partners at NOAA, called their long-time collaborator Bob Yokelson of the University of Montana, who has been studying wildfire smoke for almost 30 years. A rangy former firefighter from Montana, Yokelson helped lead the initial version of FIREX-AQ. Up until 20 years ago, he says, field research on wildfire smoke was done only by him and a few other college professors who rented a Twin Otter, loaded it with instruments and tooled around the edges of smoke columns. They were interested in the same aerosols, particulate matter and gases getting attention from FIREX-AQ, but their measurements were far coarser. Yokelson was exaggerating the field's simplicity, but the assets needed to run a comprehensive project had never been deployed. It was simply way too expensive and risky. "We were flying blind into the future," Yokelson said.

After a string of historically severe smoke seasons clarified that



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INSIDE THE CABIN of the DC-8 (1). Post-doc Xu Lu adds liquid nitrogen to a mass spectrometer used to measure a suite of gases abundant in wildfire smoke (2). Wing-mounted particle counters (3). When opened during flight, the MASTER instrument images the fire through smoke (4). At base, Ph.D. candidate Vanessa Selimovic prepares air-sampling canisters (5).

the age of fire had arrived, millions of dollars in funding for major research campaigns followed. In addition to the DC-8, which could fly at high elevations and over a great range, the FIREX-AQ team outfitted nimble prop planes with air-quality sampling instruments to fly lower and closer to columns, as well as rural communities inundated with smoke. They similarly outfitted trucks for sniffing smoke on the ground. On the jet, they deployed lasers of different wavelengths to map a smoke column in three dimensions in real time; there was an instrument to sense acetonitrile, a chemical known to be an indicator species of biomass burning, while other sensors looked for black and brown carbon, submicron aerosol composition, and a long list of other components. This compilation of tools would measure particles and gases in as many forms and sizes as the state-of-the-art technology could capture.

By determining at a finer resolution what is in smoke and the processes by which its nastier products form, air-quality forecasters could better predict the impacts of wildfire emissions on human health. Knowing how smoke differs between types of fires could also ease the burden of fire management, specifically when it comes to lighting prescribed burns. These controlled, lower-intensity fires mimic natural ones and are lit to reduce the amount of fuel available for future wildfires. They are also notoriously hard to ignite for social, environmental and regulatory reasons. The EPA stringently regulates smoke from prescribed fires, despite the fact that no field studies have demonstrated that emissions from lower-intensity burns are just as toxic as those from raging wild flames.

"When it comes to smoke in the sky, it's pay me now or pay me later," Soja says. She means that whether managers choose to

ignite fires on their own terms or let nature decide when fire-adapted landscapes burn, the skies will be smoky. Yet some kinds of smoke might be worse for human health than others. "We've got to get an understanding of emissions factors so that people can make better decisions in the field."

THE VARIABILITY OF VOCs

IN THE FALL OF 2016 the FIREX-AQ team went to Montana's Fire Lab to start peeling back the layers on emissions. To figure out what became of smoke downwind and how it produced noxious aerosols and ozone, they had to understand its contents at the ignition point. Maybe certain plants, when burned, created smoke with more ozone and PM 2.5 than others?

The team collected ponderosa pines from Montana, lilac shrubs from California, oak from Arizona and 18 other groups of species regularly burned in the West. They dried and weighed the plants, then spread them onto chicken wire woven underneath a massive ventilator hood. They lit two fires with each fuel type: a smoldering burn where the rising smoke seemed viscous like lava and a hotter burn where the smoke stood up with the fire in salute.

What they found, surprisingly, was that the fire's temperature dictated emissions far more than did the kind of plant that was burning. Certain volatile organic compounds (VOCs) were emitted during low-temperature burns, whereas others showed up mostly during high-temperature burns. The fire's temperature could be used to predict about 80 percent of those emissions, results that were published in 2018 in *Atmospheric Chemistry and Physics*.

For some of those burns, the researchers captured smoke sam-



EQUIPMENT at the base of operations in Boise, Idaho (1).
Mission scientists Carsten Warneke (left) and Jim Crawford (2).

ples and stuck them into a Teflon sack lit by ultraviolet lights to simulate sunlight. They were interested in PM 2.5, which is emitted by all fires. Long-term exposure can be deadly, even when levels are below EPA limits. In 2017 and 2018, more than 10 million people in the West were exposed to levels of PM 2.5 that exceeded the EPA's air-quality standards. In 30 years that number is expected to be closer to 82 million. By 2100 chronic inhalation of wildfire smoke is projected to kill 40,000 people annually in the U.S. alone.

In the sacks, the initial output of PM 2.5 dissipated quickly and particle levels decreased—as expected. But in some experiments, after several hours certain chemicals began to condense. Like beads of mercury pulling together, other particles settled on these growing surfaces until PM 2.5 levels that had dipped just hours before blossomed in a new form. Warneke was not sure what process explained the re-formation of PM 2.5, but he thought he had found a starting point. It increased most often in the presence of catechol, a large molecule in a building block of wood that was emitted by smoldering fires. Most intriguing about this discovery was the idea that if they linked a fire's temperature to PM 2.5 production, it might then be possible to forecast a fire's PM 2.5 output from satellites that already measure fire intensity. He and Matt Coggon, a research scientist at NOAA, also found that catechol may play a key role in ozone formation related to wildfires.

Ozone decreases lung function after repeated exposure. It is not a direct emission of wildfires; rather it forms when nitrogen oxide, VOCs and sunlight mix in the right proportions. There are always VOCs in smoke, and sunlight is a close associate of flames. But nitrogen production in wildfires is nuanced. Smoldering burns release ammonia, a nonreactive form of nitrogen, from plants.



Hot burns release nitrogen oxide, which is volatile. “The tricky thing is that the chemistry in a plume is pretty hot,” Coggon says. “It’ll transform even within an hour on big fires into something that is very different from what was emitted initially.”

The reasons for these shifts have been well understood for almost 20 years. In big wildfires, nitrogen oxide released from

plants by flames is entrained in smoke and wafted into the upper troposphere by the fire's heat. As it climbs, some of the compounds react with radicals until, after a cascade of reactions, what started as nitrogen oxide can become peroxyacetyl nitrate (PAN), a relatively stable molecule when the temperatures are cool enough. As long as the smoke continues to drift in the cooler temperatures of the upper troposphere, the nitrogen is locked up and the ozone production process is essentially frozen.

But when the smoke begins to sink again into the warmer temperatures at lower elevations, the PAN breaks down and nitrogen oxide returns. Suddenly, hundreds or even thousands of miles downwind from the fire, ozone can form in volumes toxic to humans. This helps to explain why, during certain wildfire events, ozone levels spike in Midwestern or even Eastern cities when plumes born in the West drift eastward. Urban areas, already rich in nitrogen oxide from cars and industry running on fossil fuels, can jump way past their air-quality exceedance when wildfire emissions blow into town on a hot summer day. These conditions gave Seattle the world's worst air quality at several points in 2018.

What Coggon and Warneke wanted to know is if there are other molecules emitted by fires that play a similar role as PAN. During their lab studies, they found catechols, the precursors to nitroaromatics, which, oddly enough, are used to treat coughs. At first it was not a particularly interesting find—just another molecule among the hundreds of VOCs they had identified. But in the two years after the lab work, Coggon developed a chemical model that suggested nitroaromatics could play a key role in nitrogen's life cycle and therefore in ozone's formation. "When they were there, there was less ozone," he says.

After looking at what he called back-of-the-envelope calculations based on the model runs, Coggon suspected wildfires should produce significant volumes of nitroaromatics. These molecules had never been investigated in this context. Thus, by modifying an existing tool, Warneke and Coggon developed a device to analyze the concentration of molecules in the air every tenth of a second. Called a proton-transfer-reaction mass spectrometer and small enough to fit in a rack on the DC-8, this was the instrument that tipped Coggon off to something remarkable during the flight.

SIGNALS IN THE SMOKE

"WE'RE GETTING INTO IT! We're getting into it now!" Crawford said over the plane's communication system as the DC-8 began to shake and beep. An hour and a half after leaving the North Hills Fire in Montana, the DC-8, pitched into a steep descent, had arrived at "GO HERE NOW": the 14,000-acre Tucker Fire in the shadow of Mount Shasta. When the plane entered the plume, the light went orange and the smell of wood smoke filled the cabin.

Coggon sat behind the plane's left wing staring at a screen with data from the spectrometer. The chart measured the molecular composition of hundreds of different VOCs, but Coggon's eyes were fixed on catechol, which was now at very high volumes and ticking down rapidly. "This is even more stuff than we saw two days ago!" he said. The spectrometer could not detect any nitroaromatics—just their precursor compounds. But Coggon had his suspicions about where the catechol was going. Suddenly, he was on his feet, tottering between quakes of turbulence to Wyatt Brown, a graduate student about a third of the way up the cabin. Brown was running an instrument that could detect what Coggon's could not: submicron aerosols such as nitroaromatics. "Are you seeing it?"

Coggon asked. Brown pointed to the screen—nitrocatechols, a type of nitroaromatic, had been unambiguously detected.

Coggon's reaction was too colorful to print. Although he was witnessing real-world confirmation of the chemistry he had seen in the models, the troves of novel data were just the start of a knotty process. Coggon later guessed it would take two years and further studies to determine whether nitrocatechol was a nitrogen reservoir that, like PAN, locked up the element temporarily and delayed ozone production, or whether it sequestered it permanently, halting the formation of ozone. Either theory had potentially profound implications for forecasting ozone production from smoke and therefore smoke's impact on people.

Over the course of the campaign, such riddles grew common. There was the house fire they had accidentally measured while trying to sample biomass burns in Kansas, a case study that may end up being particularly useful considering the increasing regularity with which wildfires burn human infrastructure. There was the low-intensity controlled fire in Florida's pines that produced gluts of ozone almost immediately after ignition, in contrast to a high-intensity wildfire in Washington that appeared to produce almost none. Warneke guessed, and hoped the data would bear out, that the variability was from the Florida fire burning nitrogen-rich fuels on a bright sunny day with low smoke, whereas in Washington, where the smoke reached 31,000 feet, chemical reactions had been prevented by a column too dense for sunlight to penetrate. Perhaps most vexing of all was the secondary formation of PM 2.5. On several fires they observed the volume of PM 2.5 dipping before increasing again. Were the same processes they observed in the lab also at work in nature?

After an hour of crosshatching the Tucker Fire's plume, the sun dipped behind the Pacific Ocean. Out the jet's window, the fire was still visible on the ground, a long orange ribbon snaking through the blackness. The DC-8 was running low on fuel. The pilots banked a turn east toward Boise, and Crawford finally left the cockpit. "As an individual emissions event, this was a drop in the bucket," he said. "But the details we can extrapolate from here are going to be really valuable."

Soon the scientists would turn to the less thrilling tasks of organizing the data and preparing papers that might tune modeling and forecasting tools focused on health. On the distant horizon those tools could "ideally ease regulations to make it easier to light more prescribed fires," Soja explained. But that night, awash in the smell of smoke, the scientists shook hands and exchanged congratulations. Somebody joked that Warneke had better have a Gatorade bath ready for the team when they landed. ■

MORE TO EXPLORE

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FROM OUR ARCHIVES

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ANTISENSE THERAPY

Finally Making Sense

A long-disdained therapy that targets RNA
is achieving spectacular success

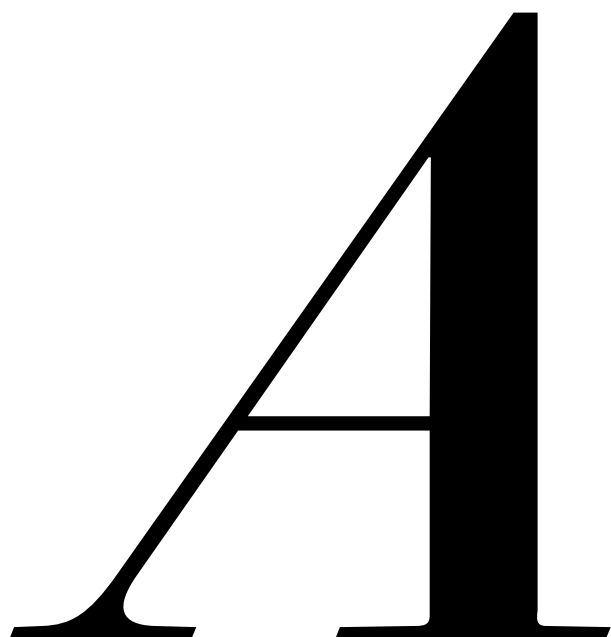
By Lydia Denzworth

Photographs by Ethan Hill

ONE OF THE FIRST children
ever to benefit from an anti-
sense drug, Emma Larson, at
her home in Long Island, N.Y.



Lydia Denworth is a Brooklyn, N.Y.-based science writer and a contributing editor for *Scientific American*. She is the author of *Friendship: The Evolution, Biology, and Extraordinary Power of Life's Fundamental Bond* (W. W. Norton, 2020).



AT HER FIRST BIRTHDAY, EMMA LARSON WAS NOT WALKING or standing, but neither are plenty of other kids at that age. She loved the bouncer her parents set up in their Long Island, N.Y., home, and she crawled with gusto. Then, at 13 months, Emma's legs stopped working. Her mother, Dianne Larson, snaps her fingers and says, "It was like that." Emma stopped bouncing. Her legs buckled when she pulled herself up to stand. The change in her crawling was subtler, but when her parents looked at an old video, the difference was obvious—Emma now covered less ground and struggled to hold her head up.

After a barrage of testing, in July 2014 the Larsons learned that Emma had spinal muscular atrophy (SMA), a potentially deadly neurodegenerative disease that strikes mostly children, robbing them of the ability to walk, talk and, in the worst cases, breathe. Her motor neurons were dying because of a severe lack of a protein called SMN (survival motor neuron) in her body. "You go through the darkest of dark periods," Dianne says. But the family was determined to "go down swinging," says Matt Larson, Emma's father. "We were willing to do pretty much anything to combat this terrible disease."

Not far from the Larsons' home, at Cold Spring Harbor Laboratory, biochemist and molecular geneticist Adrian Krainer was engaged in the same fight. He had been investigating the genetic underpinnings of SMA since 2000 and knew the problem was a missing or mutated essential gene, *SMN1*. But he also understood that people carry an inactive and potentially salvageable

analogue of that gene, *SMN2*. By 2004 he had joined forces with Frank Bennett of Ionis Pharmaceuticals to try to create a drug capable of altering *SMN2* in SMA patients so that it could ultimately generate functional SMN protein, with the aim of ameliorating the progression of the disease. To that end, the researchers turned to something called antisense oligonucleotides.

First conceptualized more than 40 years ago, antisense oligonucleotides (ASOs) are short strings of chemically modified DNA or RNA (*oligo* in Greek means "few," and nucleotides are the structural units that make up DNA and RNA). ASOs are designed to home in on the RNA strands produced by a problematic gene and alter the gene's expression. That is, the ASOs bind to a section of the targeted RNA to produce (or, in some cases, stop the production of) proteins whose absence (or presence) causes an ailment. For decades scientists had labored to prove that this strategy could yield a drug capable of treating or preventing dis-

IN BRIEF

Antisense oligonucleotides (ASOs) are short strings of chemically modified DNA or RNA designed to alter the proteins produced from specific types of RNA.

After decades of struggle, the technology may finally be achieving its full potential. Antisense drugs seem

to be particularly effective against rare neurological ailments of genetic origin.

Prion disease, resulting when a protein called PrP misfolds—creating a template that prompts more PrPs to deform—kills neurons faster than

any other neurodegenerative illness.

Using ASOs to reduce the density of PrPs in the brain while it is still healthy could preclude development of the lethal disease in those with genetic susceptibility to it.

ease, but they found such serious problems with toxicity and delivery that many abandoned it. Yet the few researchers who pushed on overcame the obstacles just in time to benefit from the detailed information about genetic diseases revealed by the genomics revolution. “Antisense is tailor-made for diseases that have a genetic cause,” says Brett Monia, who took over as CEO of Ionis in January from founder Stanley Crooke. “It’s the epitome of precision medicine.”

Krainer, Bennett and their colleagues called their SMA drug nusinersen. When injected into cerebrospinal fluid, it coaxes the inactive motor neuron gene to make SMN. With Biogen, they began testing the drug in human clinical trials in 2011. The Larsons enrolled Emma the day she was eligible: her second birthday. By then she could no longer crawl at all. Her first dose, in March 2015, was followed by two more doses in quick succession.

In May 2015 Dianne was in her bedroom while Emma was in the den nearby. “I hear her calling me, and it’s getting closer and closer,” Dianne remembers. “Next thing you know she’d crawled from the den all the way to my bedroom.” Dianne asked herself, “Did I just see this?” She picked her daughter up and carried her back down the hall. Then she returned to the bedroom and called, “Emma, come here.” The little girl crawled into her mother’s arms. Weeping, Dianne thought, “We’re on to something here!”

Indeed, they were. The clinical trial for nusinersen proved so successful that it ended a year early. The U.S. Food and Drug Administration approved the drug, under the brand name Spinraza, in December 2016. More than 8,400 patients in 40 countries are now taking it. Twenty-five newborns with the most severe SMA mutation were given the drug at birth. They are four years old now—and developing normally. “If I had done nothing else but develop Spinraza, it would have been enough,” Crooke says.

But Spinraza is also exhibit A in support of the argument that ASOs are finally achieving their full potential. It is the first ASO to boast such dramatic results and commercial success. The drug earned Krainer and Bennett the multimillion-dollar 2019 Breakthrough Prize. It also put in reach a tantalizing set of neurological targets such as Huntington’s disease and amyotrophic lateral sclerosis (ALS). “We discovered the genetic basis for most of these diseases back in the 1990s,” Bennett says. “It’s taken us 25 years to translate these really important scientific discoveries into potential therapeutics. [With Spinraza,] it was breathtaking almost to



DIANNE AND MATT LARSON with their seven-year-old daughter, Emma. “We’re on to something here!” wept Dianne in 2015, when Emma, who suffers from spinal muscular atrophy (SMA), was able to crawl to her within months of receiving the antisense drug nusinersen (brand name Spinraza).

realize that we had a technology that could have such a broad impact on patients who have no therapies available to them.”

Like long-distance runners who have been training at altitude, antisense scientists have put in hard miles to optimize the chemistry and delivery of oligonucleotides. Now they are at sea level and sprinting. More than 100 drugs are in the development pipeline for everything from Alzheimer’s disease to hypertension. Not all will reach the finish line, but, including Spinraza, eight have been approved so far in the U.S. and Europe, all for rare diseases. Drugs for Huntington’s and ALS are in the final stages of clinical trials. In a historic first, a doctor at Boston Children’s Hospital



created a custom antisense drug for one little girl with an ultra-rare disease in less than a year. “People have been talking about biologic therapies for 30 years, and what’s extraordinary is it’s starting to happen,” says neurologist Robert Brown of the University of Massachusetts Medical School, who is a leader in ALS research. (Biologic drugs are those made from living organisms.) “This is a true game changer.”

SENSE AND ANTISENSE

DNA PROVIDES THE BASIC BLUEPRINT for life, but it has to be read and translated into action through the production of proteins, which carry out most of the work in the body. Because the instructions encoded in DNA are so critical, the process of translation has protective mechanisms built into it. There is a lot of repetition, beginning with the two strands of nucleotides that zip together to form DNA’s double helix. One serves as a template, laying down sequences of the four bases that make up DNA molecules: adenine (A), thymine (T), guanine (G) and cytosine (C). The other strand reads that template and lays down a complementary set of bases. Each base on a strand is always positioned opposite its specific partner: A always pairs with T, and C with G. To ensure accuracy, the RNA only ever encodes the instructions in the nontemplate strand for the creation of proteins. Biologists call the two strands by a variety of names, including sense and antisense, which gives the ASO technology its name.

Occasionally the end results—the proteins—do not come out right. They can be overproduced or underproduced, resulting in

EMMA PLAYING on a swing set near her home. Thanks to the success of clinical trials of nusinersen involving her and others, more than 8,400 SMA patients around the world are now taking the drug. The breakthrough has spurred the field of antisense therapy, which seems to be particularly effective for neurological ailments of genetic origin.

disease. Small-molecule drugs, which make up the majority of pharmaceuticals on the market, target the proteins associated with diseases. Monoclonal antibodies, the other major class of drugs, generally bind to proteins and stimulate a patient’s immune system to attack them. In contrast, the aim with antisense drugs is to disrupt the process earlier. They are designed to replace faulty RNA during the transcription process by snapping into place according to the standard base-pairing rules and thereby tweaking protein production.

A parallel effort has focused on what is known as RNA interference, or RNAi. This technology was discovered just when antisense had been given up for dead, so its proponents avoided the term, but the drugs derived from the two approaches are related. “I think of antisense as the genus and RNAi as a species,” Bennett says. The difference is that RNAi drugs have two strands, whereas ASOs have only one. But any chain that is short—usually 15 to 20 nucleotides—is considered an oligonucleotide.

The versatility of oligonucleotide drug technology derives from the way it separates two critical elements: the platform or

molecular properties that determine drug delivery and distribution into tissues, and the sequence of bases necessary to target a specific gene. Different sequences of bases make the information contained in the drugs distinct, but antisense drugs with the same chemical modifications tend to behave in similar ways in the body. “That’s what allows us to move quickly once a platform is established to deliver to a tissue of interest,” says Jonathan Watts, a nucleic acid chemist at the University of Massachusetts Medical School. “By shuffling the sequence of bases, we can dial in a totally different target using the information from a genome-sequencing experiment of a patient with a rare disease or from the genome databases. Being able to use that information intuitively and rationally is very powerful.”

A LONG-DISTANCE RUN

THE IDEA OF USING GENETIC information to make a drug that could bind to RNA has been around since 1978. But there were a host of unanswered questions: How do you make an oligonucleotide into a drug? Why would binding to RNA produce an effect? Nonetheless, the idea was intriguing enough to Crooke that in 1989 he left his position as head of research and development for SmithKline (now GlaxoSmithKline) to establish a company dedicated to the development of antisense technology. He was joined there by his wife, Rosanne, also a pharmacologist, and by colleagues, including Bennett and Monia. (Originally called Isis, the company eventually changed its name, for obvious reasons, to Ionis Pharmaceuticals.)

A handful of other companies started up to pursue antisense around the same time, but one by one they abandoned the hunt. The leader of one, Michael Riordan of Gilead Sciences, announced in 1995 that antisense did not work. For a time it did seem that the problems of toxicity, off-target effects and a lack of potency might not be overcome.

But Crooke and his colleagues doggedly solved the scientific problems one at a time. A long, high wall of patents at Ionis’s headquarters near San Diego attests to their work. First they had to develop the necessary chemistry. For example, by modifying a key position (2’) in ribose sugar in the RNA and DNA of ASOs, they were able to enhance the affinity of the ASOs for RNA receptors, thereby dramatically reducing the necessary dose. Other chemical modifications improved safety and tolerability. They also found that the drugs were not taken up into tissue when delivered directly into cells in culture, but Ionis scientists made the leap to testing the drugs in animals anyway. Monia, who ran drug development for Ionis, vividly remembers the moment when he looked at a chemical test he was using to measure levels of a specific RNA and saw almost no trace of it—the drug had entered cells in most tissues, and they had successfully knocked down the RNA’s expression.

Time spent working on cancer did not prove all that fruitful, Bennett says. (Promising, more carefully designed experiments are in the pipeline, however.) What did work were drugs with specific targets, usually for rare diseases, for which proof of concept is easier to establish. The earliest ASOs were for diseases of the eye and, later, the liver, where uptake works particularly well. The drugs were effective, but they were ultimately not commercially viable, because better solutions came along.

The newest oligonucleotide drugs are designed to tackle rare diseases. One is Exondys 51, which targets Duchenne muscular dystrophy, a severe, progressive degenerative disease caused by

mutations in the gene that produces the protein dystrophin. Annemieke Aartsma-Rus of Leiden University Medical Center in the Netherlands, who is president of the Oligonucleotide Therapeutics Society, is an expert in Duchenne and helped to develop the drug. It has been less spectacular than Spinraza, but on the strength of early results showing increased dystrophin levels, the drug received accelerated regulatory approval. The company marketing it (in which Aartsma-Rus has a stake) will need to show by 2021 that it makes a meaningful difference in how a patient functions.

The first RNAi drug, Onpattro, made by Boston-based biotech company Alnylam Pharmaceuticals, was approved in 2018 for treating a hereditary form of nerve damage. An approved Ionis ASO drug called Tegsedi treats the same thing. The focus now for all oligonucleotide therapies is delivering more drug more productively to more parts of the body. “A lot of people were in wait-and-see mode,” Aartsma-Rus says. “They now see that if they don’t start, they’ll have missed the boat.”

HOPE FOR THE BRAIN

FOR A LONG TIME ANTISENSE companies largely ignored neurological targets because oligonucleotides generally do not cross the blood-brain barrier. But Bennett thought that delivering them directly to the cerebrospinal fluid via lumbar puncture might work. He pushed a skeptical Crooke to let him try. “I had a lot of reservations, but the idea is to say yes,” Crooke says. “‘No’ never made a drug, and ‘no’ never made anybody better.” They started exploratory studies with a mouse model of Huntington’s, an obvious candidate for ASOs because it is directly linked to a specific mutation. People with Huntington’s carry a repeated sequence of a triplet of base pairs, CAG, that results in toxic levels of huntingtin protein and causes the progressive breakdown of brain cells. In mice, Bennett and his colleagues found that they could reduce levels of the mutant protein. “The mice actually improved,” Bennett says.

Meanwhile Krainer was investigating SMA. Others had discovered that healthy people have two versions of a critical motor neuron gene, *SMN1* and *SMN2*, but the latter makes very little functional SMN protein. People with SMA do not have a functional *SMN1* gene, and their broken copy of *SMN2* cannot do the job itself. Stretches of DNA include both “exons,” the coding sequences that are expressed (hence the “ex” in their name), and “introns,” the noncoding stretches between exons. A process called RNA splicing joins the exons together and discards the introns. The *SMN2* gene had a variation that rendered it inactive by causing a particular coding chunk, exon 7, to be ignored. Krainer and Bennett surmised that an ASO could force that instruction chunk to be included. By 2008 they had shown that the ASO they had created worked in mice by fixing the splicing defect. The clinical trials in humans followed.

“This is what’s called a disease-modifying therapy,” Krainer says of Spinraza. “It isn’t just dealing with some symptoms. It’s getting at the root cause of the disease and changing its course.” Early intervention is critical. A person with symptoms, such as Emma Larson, has already lost some motor neurons, which cannot be restored. But the treatment can prevent the remaining neurons from dying off and bring improvements in motor function. The success in treating infants has led to a push for newborn screening for SMA, which now occurs in 16 states.

“The closer you start the treatment relative to birth or disease onset, the more you can achieve,” Krainer says.

Spinraza’s clinical success showed that, contrary to expectations, antisense therapy could be particularly effective against brain diseases. Neurological targets have “become the low-hanging fruit,” Aartsma-Rus says. Several ASO-based therapeutics are in development for Huntington’s, for example. One, known as RG6042, developed by Ionis and Roche, is in a phase 3 clinical trial. Earlier safety and tolerability studies showed that it is possible to lower levels of mutant proteins, says Scott Schobel, clinical science leader of the global Huntington’s ASO program for Roche, but “what now is the clinical import of that?” The current trial should answer that question. “We would consider even a 30 percent slowing of decline a victory,” Schobel says. That would amount to giving patients three to four months back out of a year while they are still functional.

Also known as Lou Gehrig’s disease, ALS is more complicated because at most 10 percent of cases have a clear genetic cause that runs through families. The most common inherited form is caused by a mutation in a gene called *C9orf72*; another gene, *SOD1*, causes about 20 percent of familial cases. Those make up a fraction of all cases, but the promise of antisense has injected new hope where there was previously little. “My mood is sky-high,” says ALS researcher Brown, who led the team that identified *SOD1* in 1993. Clinical trials for antisense drugs to treat both the *C9orf72* and the *SOD1* forms of the disease are underway. The drugs have proved safe and tolerable and suppress the activity of mutant proteins.

Part of what has clinicians such as Brown so excited is that antisense has also made it possible to develop drugs for individual patients. A young Iowa woman named Jaci Hermstad, who has a very rare form of ALS caused by a mutation in a gene called *FUS*, began taking a drug tailor-made for her in the summer of 2019. So far she is tolerating it well, and there have been small improvements, such as her regained ability to move her arm.

A DRUG FOR MILA

A DRUG FOR JUST ONE PERSON was science fiction until neurologist Timothy Yu of Boston Children’s Hospital created a drug in less than a year (record time) for Mila Makovec, now nine years old. Mila has an ultrarare condition called Batten disease, which is really a family of disorders in which mutations cause buildups of proteins and lipids in cells. Children with Batten rarely survive into adolescence.

Like many people with Batten, Mila was unusually well coordinated and verbal early on. But at three, her toes started turning inward. Between four and five, she got clumsier and started losing her vision. Doctors at Children’s Hospital Colorado eventually connected Mila’s symptoms with one gene mutation for Batten that she carried.

But Batten requires two gene mutations. Mila’s mother, Julia Vitarello, went looking for someone who could fully sequence Mila’s genome to confirm the diagnosis. She and Mila’s father also wanted to know whether their younger child, Azlan, was at risk. In January 2017 her plea reached Yu’s wife via social media.

Yu’s team did the sequencing and found the missing second mutation. It was caused by a jumping gene, or transposon, a sequence of nucleotides that replicates and moves to a spot in the genome where it does not belong. The discovery meant Azlan was

safe. It also gave Yu an idea: it might be possible to create a drug for Mila. “We realized we could pull the Spinraza trick,” Yu says. “But instead of using an antisense oligo to force an exon that was being ignored to be included, we were using an antisense oligo to shut down an exon that was getting in the way.”

After several pharmaceutical companies demurred, Yu oversaw manufacture of the drug himself. Some of the \$3 million Vitarello had raised in search of a cure went to the project (she prefers not to specify how much). Yu called the drug milasen, for the only patient who would receive it, and Mila got her first dose in January 2018. By then she was blind and having seizures 20 to 30 times a day, some lasting for several minutes. The damage already done to Mila’s body cannot be repaired, but with treatment her seizures soon eased. After four or five months, they were lasting only a few seconds rather than minutes. Vitarello says that recently, with her help, Mila even walked up stairs with alternating feet.

When Yu reported Mila’s story in the *New England Journal of Medicine* late in 2019, it made headlines. It also raised concerns about the cost and the ethics of developing a drug for one person. (Both Yu’s institutional review board and the FDA approved milasen.) Bioethicist Sara Goldkind, a former FDA staffer, as well as a consultant on rare disease programs and an adviser on milasen, says that process is critical in such an unusual situation. Tests for safety and effectiveness must still be done, but there are also many mitigating circumstances—these are rare, deadly and rapidly progressing diseases with no treatments—that might allow the FDA to rely on a single adequate and well-controlled study instead of the two usually required. “There needs to be some flexible thinking in terms of how the regulations are applied,” Goldkind says.

Crooke, who has stepped back from running Ionis day-to-day, set up a foundation to support the development of customized antisense drugs for ultrarare diseases affecting too few people to be viable commercially. Vitarello and Yu, too, hope to make personal treatments available to all children like Mila. One of the great advantages of antisense is that such individualized drugs can be created not just quickly but also relatively inexpensively, despite the considerable sums spent on Spinraza and milasen.

EMMA THE FLAMINGO

LIKE MILA, EMMA LARSON was not cured. The neurons she lost have not been replaced, and she has skeletal changes that are likely to be permanent. At the Larsons’ home, there are wide expanses of uncarpeted wood floor, the better for Emma, who just turned seven, to zoom around in the wheelchair she calls her race car. She is in first grade, and her favorite part of the day is recess, when she likes to play on the slide and the seesaw.

When the wheelchair is parked, her parents carry her from room to room. She crawls around her playroom to show off her favorite toy, a Polly Pocket Mall. But with her walker and braces attached to a pair of sparkly pink sneakers, Emma can take a few steps under her own power. And in the dining room, with one hand on the table, she stands on the bench along the wall like a flamingo and cries, “Hey, look, standing with one leg!”

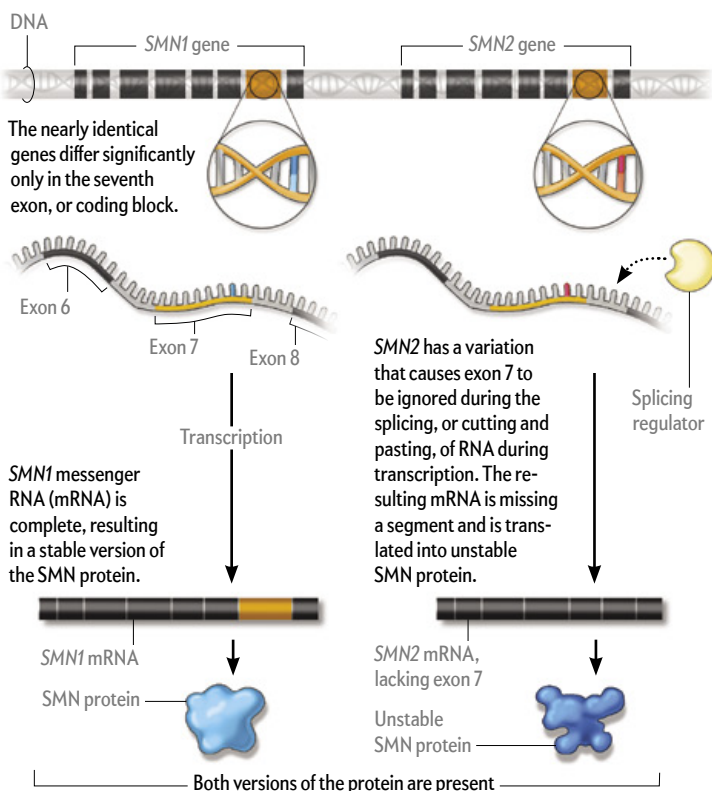
Life is still hard, the Larsons admit, but they no longer despair. They hope Emma can live independently. And they are thrilled that the newborns on Spinraza are doing so well. “That made my heart full,” Dianne says as her eyes well up. “In some regards, it’s a little late for Emma, but she helped pave the way for those little babies.” ■

Nusinersen, Antisense's Dramatic Success Story

Antisense oligonucleotides, or ASOs, are short segments of DNA or RNA designed to bind to messenger RNA and alter the transcription of DNA into proteins. After decades of struggle, researchers have achieved spectacular results with nusinersen, which arrests the progression of spinal muscular atrophy, a lethal neurodegenerative disease, by prompting a nearly inactive gene to efficiently make a vital protein.

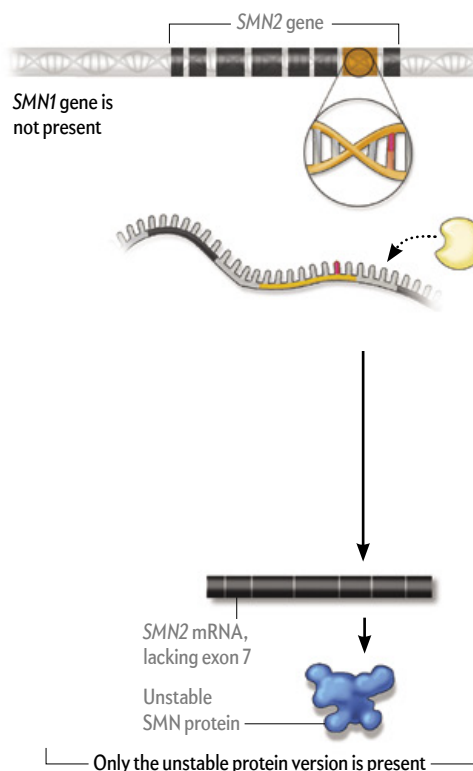
In Healthy People ...

Normally a person has two versions of the gene for producing SMN. The first gene, called *SMN1*, produces a stable version of the protein SMN, whereas the second, *SMN2*, generates an unstable version.



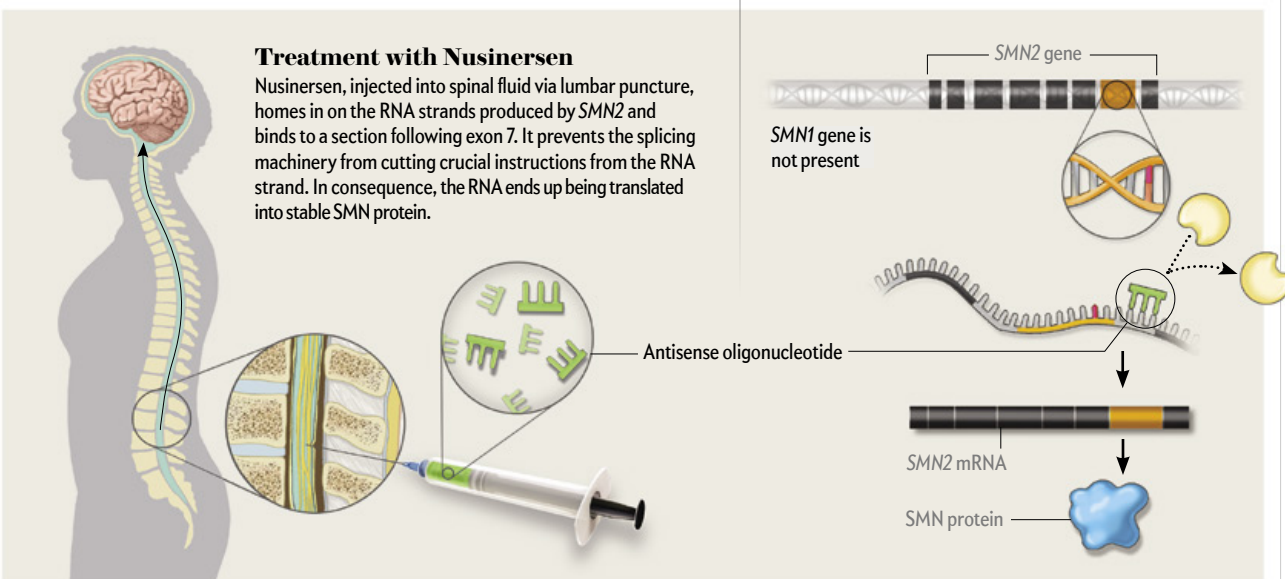
In People with SMA ...

Patients with spinal muscular atrophy are missing the gene *SMN1*. They do have *SMN2*, but it produces far too little usable protein.



Treatment with Nusinersen

Nusinersen, injected into spinal fluid via lumbar puncture, homes in on the RNA strands produced by *SMN2* and binds to a section following exon 7. It prevents the splicing machinery from cutting crucial instructions from the RNA strand. In consequence, the RNA ends up being translated into stable SMN protein.





AUTHORS at their laboratory for researching prion disease at the Broad Institute in Cambridge, Mass.

ANTISENSE THERAPY

Preventing *Prions*

Treating susceptible individuals
while they are still healthy
offers the best hope for warding off
a deadly brain disease

By Sonia Minikel Vallabh and Eric Vallabh Minikel

Sonia Minikel Vallabh and **Eric Vallabh Minikel** run a research laboratory at the Broad Institute of MIT and Harvard dedicated to developing a treatment or cure for prion disease. The couple changed careers to become medical researchers after they learned that Vallabh is at high risk of developing the fatal illness.



NO ONE EXPECTS TO LIVE A BEFORE-AND-AFTER KIND OF LIFE, DIVIDED into the moments before and the moments after a single defining event. When the two of us met, fell in love and got married in Sonia's backyard in Hermitage, Pa., we had no idea we were in our "before" life. We had no intention of quitting our careers in law and engineering and taking entry-level jobs in a different field. We could not have imagined the scramble to learn an entirely new discipline from scratch nor a day when we would defend back-to-back our doctoral theses in biomedical research—our presentations intercalating to form a vision for a first-ever treatment for a fatal neurodegenerative disease.

We abruptly entered our "after" life on October 9, 2011, when Sonia learned that she was at risk for a rare DNA mutation that would make her all but certain to die young of a rapidly progressive brain disorder: prion disease. This illness occurs when a protein called PrP that is normally present in our brains changes shape into an abnormal form, called a prion. (Confusingly, the normal version of the protein—PrP, or prion protein—was named *after* the deformed version, the prion, was discovered and named.) A prion causes other copies of PrP that it touches to also warp into prions. This cascade of protein misfolding spreads across the brain, killing brain cells at a rate that outstrips that of any other neurodegenerative disease.

By the end of the year, we knew that Sonia had indeed inherited the dreaded mutation. Since then, we have been on a mission. Success means keeping Sonia's brain, and those of others like her, healthy and fully functional for years or decades, hopefully for a lifetime. Failure means that in her prime, Sonia will be struck down almost overnight. Within weeks of her first noticeable symptom, she will have suffered devastating brain damage and ceased to be the person she was.

Because a single—and apparently an expendable—protein, PrP, is responsible for this disease, we have hope that current technologies can reduce its amount in the brain, depleting the fuel that enables deadly prions to spread. The trouble is the stunning speed with which prion disease progresses: our best chance of winning this battle is to act before catastrophe strikes. But prevention of disease—as opposed to intervening only after disease is underway—is not business as usual. Eight years on,

we are waging, every day, an uphill struggle to forge a new paradigm in drug development: for testing a promising drug not only for its ability to slow the progression of disease but also for its ability to keep healthy brains healthy for longer.

A YEAR OF CRISES

MONTHS BEFORE WE GOT THE NEWS, we had witnessed the progression of prion disease in Sonia's mother, Kamni. In February 2010, still in her usual good health and with high cognitive function, she went to see an ophthalmologist because of blurry vision. On March 17, when Sonia called to wish her mom a happy 52nd birthday, Kamni was unable to finish a single sentence without losing her train of thought. In May she spoke in tongues, recognized family members less than half the time and forgot that she could no longer walk—which meant that despite our best efforts, she repeatedly got up, fell and hurt herself. From June onward, she became wheelchair-bound and underwent several hospital stays. She was still able to make eye contact but began to recoil from touch, her comfort in the company of loved ones replaced by constant fear of the poking, prodding and endless needlesticks that human presence had come to imply. By July she was unable to speak, eat or sit up. Her face reflected only agony and her eyes only fear as she struggled continuously against the restraints the nurses had used to tie her hands to the hospital bed to keep her from pulling out her feeding and colostomy tubes. In August she was permanently intubated and ventilated, mute and motionless. She still had no diagnosis.

During that year, radiating outward from the primary crisis



VALLABH and Minikel with their daughter, Daruka (1). Sonia inherited a mutation for prion disease from her mother, who died of the illness—but the couple hope to develop a drug that can fend it off indefinitely. Daruka, who was screened for the mutation as an embryo and is free of it, holds a photo of her maternal grandmother (2).

were the second- and third-order crises. What do you do when a person requires more care than one person, or even one entire family, can provide? Hospitals, it turns out, are not responsible for answering this question. After the tests have been run and all possible diagnoses rejected, the patient is discharged to her home until the next inevitable complication—a head injury, pneumonia—justifies a return. Constant crisis mode, and the sudden loss of all household logistics expertise, meant that bills went unpaid, accounts were suspended, electricity turned off. And to be clear, we were the lucky ones. Of the approximately \$1 million in medical bills Kamni incurred that year, her health insurance paid for nearly everything.

In December she passed away, and we felt an emotion we had never imagined we could associate with a loved one's death: relief. It was not a saying of goodbye but a realization that we had already said goodbye. This is what dementia robs us of—not just the person we love but the present-tense goodbye.

After Kamni died, we slowly tried to put the worst behind us—but the worst was one step ahead. When we came home for a family friend's engagement party that October, we attributed Sonia's father's long silences and distant stares to heartbreak, loneliness and the long tail of exhaustion. But as we were loading our bags into the car to go to the airport, he pulled Sonia aside and delivered the news that broke our lives in two. An autopsy had revealed that Kamni's illness had been fatal familial insomnia, a type of genetic prion disease. She had had a defect in the gene for producing PrP, and Sonia was at a 50–50

risk. At the close of 2011, we learned that Sonia had in fact inherited her mother's mutation—which meant that she was all but certain to also develop prion disease. She was 27 years old.

Almost right away we decided to devote our lives to finding a cure. We enrolled in night school to learn biology, abandoned our former professions to take entry-level positions in research laboratories and in 2014 enrolled in a Ph.D. program at Harvard Medical School. Now at the Broad Institute in Cambridge, Mass., we run a prion research lab. It goes without saying that we would not go to such lengths just to keep Sonia alive in a state of profound dementia for 12 months instead of six. The goal was—and is—to keep Sonia's brain healthy for additional years or decades, if possible indefinitely. The goal is prevention.

A LETHAL FOLD

PRION DISEASE MANIFESTS ITSELF in a variety of ways, described as Creutzfeldt-Jakob disease (CJD), fatal familial insomnia, bovine spongiform encephalopathy (BSE or “mad cow” disease) and others. Many of its names were assigned long before neurologist Stanley B. Prusiner made his Nobel-winning discovery in 1982 that a single causal agent—a protein—unifies them. Though most infamous for the fewer than 1 percent of human cases that are acquired by infection (such as via contaminated meat), most cases of prion disease arise randomly. A PrP molecule in someone's brain spontaneously assumes an abnormal configuration or folding pattern, setting off a rapidly escalating chain reaction. In contrast to such “sporadic” prion disease, about 15 percent of

cases are caused by mutations in *PRNP*, the gene that encodes PrP. For reasons we do not fully understand, these mutations make the protein far more likely to misfold. Whereas a person with two normal copies of *PRNP* has a chance of about one in 5,000 that the PrP proteins in his or her brain will spontaneously deform in his or her lifetime, someone with Kamni's mutation has a risk of more than 90 percent.

The *PRNP* gene is located on the short arm of chromosome 20 in humans. It comprises 15,000 base pairs, of which 762 encode the protein—which, in its final form, is a chain of 208 amino acids. Most variants that give rise to genetic prion disease are changes of a single base in *PRNP*, which alter just one amino acid in the resulting PrP molecule. Sometimes a repeating segment of the gene expands, leading to a longer version of PrP.

In its normal conformation, about half the length of the normal protein is well ordered, consisting mostly of “alpha helices,” spiraling structures common in proteins. At the far end of this section, PrP has a sugar anchor that links it to the outer surface of a cell membrane, its native habitat. (One pathogenic variant of the gene generates a foreshortened PrP, lacking an anchor to the cell membrane.) The other half of the protein is disorderly, forming a floppy tail that hangs off the cell surface and into the space between cells.

Although researchers do not fully understand the shapes of prions, we do know that the misfolded form generally has more “beta sheets”—stacked and pleated strands of amino acids—than alpha helices. In this form, the protein is more resistant to being broken down by enzymes. What makes this shape a prion (proteinaceous infectious particle) is that it can serve as a template, prompting other copies of PrP to also link up and misfold. A cascade of prions spreads through the brain, forming fibrils and aggregates and killing nerve cells by mechanisms that remain unclear.

Prions also come in different strains with different properties—such as which animal species are susceptible to them and how they present themselves clinically. Adding to the complexity, it appears that each strain may actually consist of a range of different misfolded conformations of PrP—analogueous to how a population of a given bacterium, in the context of an infection, may harbor genetic diversity that gives some members a leg up if circumstances change. This variability may explain why one drug strategy that researchers have pursued—looking for compounds that reduce the number of prions in cells—has failed. For example, the antimalarial drug quinacrine is effective against prions in cell cultures, but studies in humans, including a randomized double-blind clinical trial in 2013, have found it to be ineffective in patients. Further experiments with quinacrine and other compounds at Prusiner's lab at the University of California, San Francisco, now suggest that even if a drug depletes one of these misfolded configurations, others can rebound to yield drug resistance.

THE PREVENTION PARADIGM

ANOTHER SIGNIFICANT CHALLENGE is finding people on whom to test potential drugs. Typically clinical trials of a new drug re-

cruit sick patients to see whether those who receive the medication feel better, function better or survive longer than those who receive a placebo. But in such a rapidly progressive disease, by the time symptomatic patients are identified, they are profoundly debilitated. In the largest reported clinical trial of prion disease, which tested the compound doxycycline, an estimated half of patients were already on life support before being treated. (The doxycycline did not help.)

The core problem is the explosive tempo of the disease. Prions replicate exponentially. Even before symptoms show up, billions of prions have already filled the brain. And once they begin killing brain cells, the rate is blistering; at this point, even an effective antiprion drug may have limited ability to help. Future trials might try to screen for “early symptomatic” patients, but catching the disease early is incredibly difficult. Doctors do not even suspect prion disease until an average of three months from a patient's first symptom—by which time Kamni could no longer speak. Even a drug that halted the disease at that stage would not undo any brain damage already sustained.

We need a new paradigm in drug development: testing promising drugs not only for their ability to slow the progression of disease but also for their ability to keep healthy brains healthy for longer.

Thus, a drug that could keep Sonia healthy might do nothing in advanced patients at a symptomatic stage of illness. Tests of antiprion compounds in mice suggest that might be the case for many, even most, drugs we could develop for prion disease. One small molecule developed in Prusiner's lab, called IND24, can quadruple the life span of prion-infected mice if given prophylactically, but it does less good if given later—and it loses even a whiff of efficacy as the mice approach the symptomatic stage. The three other chemical compounds that have shown compelling efficacy against mouse strains of prions are also more effective the earlier treatment is begun.

Smart people have grappled with these questions for years when confronting Alzheimer's disease, which also features protein aggregation. Candidate drugs targeting the accumulation of beta-amyloid, the malformed protein found in Alzheimer's brains, have failed, in trial after trial, to benefit patients, leading observers to wonder if the therapeutic hypothesis is wrong or if the time of intervention is simply too late. Two approaches are being employed to test whether anti-amyloid drugs do, in fact, delay Alzheimer's if given earlier. One is to randomly assign still healthy people at high genetic risk of early-onset Alzheimer's to groups receiving drugs or placebo and follow them for years to see who develops cognitive decline. The other ap-

proach, sometimes dubbed “secondary prevention,” recruits cognitively healthy people in whom molecular evidence of the disease process can already be detected, to see whether a drug delays the progression into symptomatic disease. These molecular markers show up decades before the onset of the disease.

Neither approach appears likely to work for prion disease. Following genetically susceptible individuals to the onset of disease turns out to be infeasible because of the highly variable age of onset and the small population of patients. We and others have studied people at risk for prion disease but have not found consistent evidence of the kind of progressive pathology that precedes Alzheimer’s. Prion disease appears to be basically undetectable before dementia ensues: it is less the rumble of a freight train approaching and more the split-second glance upward as the asteroid strikes.

DEPLETING THE FUEL

WHERE DOES THIS LEAVE US? If trials in symptomatic patients may mislead and trials for prevention are infeasible, how will we show that a drug could save Sonia’s life? We have come to believe that the answer was handed to us at the very beginning of our quest, embedded in the genetic test report that changed our lives. We already know the single gene that causes this disease and the single protein fated to go wrong. The key is to target normal PrP before it ever misfolds.

If we can lower the amount of PrP produced in the brain, all evidence suggests that we will delay the disease. For example, mice producing half the normal amount of PrP take more than twice as long to develop prion disease if infected. With less PrP around, it takes much longer for the prions to replicate. Fortunately for us, PrP does not appear to be essential to brain function. Mice, goats and cows that have the gene for producing PrP “knocked out” are healthy, and so are people with one inactivated copy of the gene.

Targeted lowering of PrP in the brain may now be achievable using antisense oligonucleotides, or ASOs. These are short, chemically modified pieces of DNA, with sequences designed to target an RNA molecule of interest—and they can trigger its destruction so that it no longer produces proteins. Recently Ionis Pharmaceuticals in Carlsbad, Calif., has figured out how to develop and dose ASOs for the human central nervous system. Partnering with Ionis, we have found over the past five years that ASOs that reduce PrP levels keep prion-infected mice healthy for longer. These preclinical results, combined with clinical, genetic and other data we have gathered and the patient registry we have launched, have convinced Ionis’s leadership to undertake development of an ASO-based prion disease drug, with a goal of reaching first-in-human trials in the coming years. For the first time, a major industry player has committed to developing a rational, targeted therapy for prion disease.

If ASOs that lower PrP turn out to help patients with symptomatic prion disease, we will be thrilled. But we need to find a way for such a drug to benefit patients who are at risk, even if it only works on a preventive basis. We propose that PrP concentration in spinal fluid can serve a pharmacodynamic biomarker—a molecular measure of whether a drug has its intended effect. And that this readout can, in turn, serve as a surrogate biomarker: the outcome measured in a clinical trial when one cannot directly gauge whether patients improved. That is, we

propose to treat people who are still healthy and show that the protein that causes the disease is lowered. The U.S. has a framework for such clinical paths, called Accelerated Approval, and there are precedents—including the use of “viral load” to approve HIV/AIDS drugs.

In 2017 we took this proposal to a meeting with the Food and Drug Administration and found great enthusiasm for our preventive approach. We left with a list of homework and a new team of allies. Two years on, we have learned how to precisely measure PrP in spinal fluid and have gathered evidence that it is originating from the central nervous system. We also know that its levels are stable enough over time that we could measure a drug-dependent decrease.

FORGING AHEAD

WE STILL ENCOUNTER CONSIDERABLE RESISTANCE. At what age should we begin treating people? How will we ultimately confirm that the drug delays disease? These are important questions, and we have the tools to devise rational answers. But the level of anxiety surrounding these issues reflects just how little precedent there is for therapeutic intervention to keep brains healthy. Perhaps the biggest pushback that we get is: Will insurers pay for this kind of drug? And behind it, the larger question: Will society pay for a prescription drug for years and years for people who are not yet sick and who, if the drug works, may never get sick?

For once, the rarity of our disease may work to our advantage. Prion disease patients are rare, genetic ones more so, and those who know they are at risk before onset are yet rarer still. Our impact on an insurer’s bottom line is nothing compared with a new drug for heart disease or diabetes that millions may take. But there is a larger picture, too. We as a society need to ask what we want for our brains. If you were one of the 20 percent of people for whom neurodegenerative disease lies ahead and if you had a preventive drug, when would you take it? Would you wait until after the onset of dementia? Until mild cognitive impairment? Until an MRI showed your brain shrinking? Or would you take it before any of that happened?

In prion disease, we may have no choice. But that also means that we have an opportunity to forge a path toward the goal of prevention. For all the progress in modern neuroscience, every human brain remains unspeakably and unknowably complex, an interconnected network of almost 100 billion neurons we do not understand, cannot fix and cannot possibly replace. If you ask what you want for your brain—and the few brains that you love most in the world—you may find that your answer is the same as ours: prevention. ■

MORE TO EXPLORE

Antisense Oligonucleotide Therapies for Neurodegenerative Diseases. C. Frank Bennett et al. in *Annual Review of Neuroscience*, Vol. 42, pages 385–406; July 2019.

Antisense Oligonucleotides Extend Survival of Prion-Infected Mice. Gregory J. Raymond et al. in *JCI Insight*, Vol. 4, No. 16, Article e131175; August 22, 2019.

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FROM OUR ARCHIVES

Detecting Mad Cow Disease. Stanley B. Prusiner; July 2004.

[scientificamerican.com/magazine/sa](https://www.scientificamerican.com/magazine/sa)



WHAT IS KILLING THE



MONARCHS?

ECOLOGY

It seemed simple: Roundup herbicide was destroying America's favorite butterfly. But new evidence has started an urgent debate about other causes

By Gabriel Popkin



KAREN OBERHAUSER WAS SCRAMBLING UP A MOUNTAIN ABOUT 100 KILOMETERS northwest of Mexico City when she began to fear for the future of the monarch butterfly. It was the winter of 1996–1997, and Oberhauser, an ecologist then working at the University of Minnesota and more accustomed to the flat, low-lying U.S. Midwest, huffed and puffed during the steep, high-altitude hike. Her head ached in the thin air. But when she stopped to look around, she saw millions of monarchs draped like living jewels on fir trees that hugged the slopes.

Nearly the entire monarch population was crammed into this spot and a few forests close by—just about 18 precious hectares in total. Scientists who study the butterfly knew about the location, but this was the first time Oberhauser had been to it. One freak storm or an illegal logging operation, she thought, could wipe the place out. “It made me realize how incredibly vulnerable they are,” she recalls.

That forest is the start of a remarkable annual migration that sends monarchs as far north as Canada during the summer and brings them back to Mexico every winter. Along the way they breed and feed in Midwestern farm fields near Oberhauser’s home. And during the years after her forest visit, Oberhauser began to suspect that her region had become another monarch vulnerability. Farmers were dousing corn and soybean fields there with the weed killer Roundup to wipe out many nuisance plants. But the chemical also kills a plant precious to the monarchs: milkweed, on which adult butterflies lay their eggs and the only plant that monarch caterpillars eat. Oberhauser and her colleagues began counting plants and eggs. They concluded that fewer milkweed plants in farm fields meant fewer eggs, which meant fewer adults returning to Mexico. In 2012 she co-authored a paper announcing this “milkweed limitation hypothesis” and its alarming implication: Roundup was imperiling the great monarch butterfly migration.

The public and many monarch scientists were galvanized by the idea. It made sense—a major food source was vanishing just as Mexico’s butterfly population was crashing. In the winter of Oberhauser’s visit, there had been about 300 million butterflies, but just over a decade later there were fewer than 100 mil-

lion. The remedy, Oberhauser and others said, was to plant milkweed in large amounts to make up for the losses. Thousands of citizen conservationists answered the call. Michelle Obama planted milkweed in a White House garden. Environmental groups petitioned the U.S. Fish and Wildlife Service to list the monarch butterfly, *Danaus plexippus plexippus*, as a threatened species to give it more habitat protection.

But since then, some scientific cracks have emerged in the milkweed case. Monarch censuses taken in the U.S. both during and after the summer breeding season showed no steady decline, even as Mexican numbers plummeted. And many Mexican butterflies came from U.S. areas without many Roundup-soaked crop fields, other data suggested. Skeptical scientists asserted that the insects were breeding fine in northern climes but that something was taking them out on their way to Mexico. “The migration is akin to a marathon,” says Andrew Davis, an ecologist at the University of Georgia. “If the number of people who start the marathon has not really changed in 20 years but the number of people who reach the finish line has been going down, you wouldn’t conclude that the number of people is declining. You would conclude that something’s happening during the race.”

The identity of that something, however, remains an elusive and troubling mystery. Some data have suggested that landscapes have lost nectar-giving plants that adult monarchs feed on during their southward journey and that the all-important forests at the end of the migratory route have been degraded. Scientists have also speculated that a parasite infection might be cutting down the migrants. (A smaller monarch population that winters on the California coast has also crashed

IN BRIEF

As Roundup killed milkweeds in crop fields early in this century, scientists blamed the herbicide for a drastic drop in monarch populations. **But different suspects** have emerged, such as forest changes at the southern end of the annual monarch migration. **Now scientists**, all worried about the beloved butterfly, are arguing over the real threat and how to stop it.

recently. Entomologists are concerned about this group, but its habitat does not overlap with that of the eastern population, so scientists think the causes of this crash are probably different.)

Virtually everyone agrees that overall, despite spikes and dips from one year to the next, the winter population in Mexico has been heading down for most of the past three decades. That is not good news for the monarchs. What to do about it, though, depends on the cause. Oberhauser and her allies still contend that milkweed loss is enemy number one. But the other evidence adds confusing and complex twists to what once seemed like a straightforward story with a ready-made villain. That means helping the insects has become more complicated, too.

NORTH BY SOUTH

THE FIRST DEFINITIVE REPORT of monarchs moving en masse comes from 1857, when a naturalist described butterflies appearing in the Mississippi Valley in “such vast numbers as to darken the air by the clouds of them.”

Over time biologists learned that when spring comes to the valley, as well as to other parts of North America, female monarchs alight on more than 70 species of milkweed plants (genus *Asclepias*) to feed and to lay eggs. One adult female can lay up to 500 eggs. When that job is done, she dies. From her eggs hatch caterpillars that turn into butterflies; the cycle repeats four to five times during a year.

Monarchs that overwinter in Mexico fly north and lay eggs near the Texas border in the spring. Their offspring live two to six weeks and spawn generations that move to the Midwest and South and ultimately all the way into the Great Lakes states, New England and Canada. As the days shorten in the fall, the last butterfly generation, dubbed the “super generation,” appears. These insects can live as long as eight months because their metabolism slows down and they do not spend precious energy on reproduction. Instead they travel south—all the way from higher latitudes to Mexico, covering up to 160 kilometers in a day. By December the insects that have survived the trip are huddled on Mexican firs. They live there until early spring, when they begin their own journey north, and their children continue the odyssey.

In the late 1970s, after a long search, biologists discovered the tiny mountainside forests where monarchs were overwintering in Mexico. The late Lincoln Brower, who worked as a biologist at Amherst College and then at the University of Florida, helped to persuade Mexican officials to place the forests under protection, launching the monarch conservation movement.

In the early 2000s Oberhauser and John Pleasants, an ecologist at Iowa State University, discovered another key monarch habitat: the farm fields of Iowa and other Midwestern states, where common milkweed plants growing between crop rows were dotted with monarch eggs. Apparently the crop fields were a massive hatchery. “That was an eye-opener,” Oberhauser says. It revealed “how important agriculture really can be, even though we think about it as a biodiversity wasteland.”

Subsequent field visits by the two researchers revealed that milkweed plants in these farm fields held up to four times more eggs than did milkweed in natural prairies and in farmland set aside for conservation. “They seemed to be monarch magnets,” Pleasants says.

American farm fields were, however, about to undergo an unprecedented ecological cleanse. Agricultural chemical com-



MONARCH BUTTERFLIES need milkweed to reproduce. Adult butterflies lay their eggs on the plants (1). The caterpillars that come from those eggs will eat only milkweed (2).

pany Monsanto had engineered corn and soy plants with a gene that allowed them to survive exposure to the herbicide glyphosate, better known by its trade name, Roundup. That meant Roundup could be sprayed liberally, leaving money-making crops unharmed while killing nearly everything else in a field. For farmers, “Roundup Ready” corn and soy were boons. For other plants that took up space among harvest rows, they were a death sentence. By 2007 nearly all the farmed soy and more than half of the corn in the U.S. were Roundup Ready.

Based on their Iowa data, Pleasants and Oberhauser estimated that between 1999 and 2010 the overall number of Midwestern milkweed plants had declined by 58 percent. Brower and his colleagues had reported that within that time span, overwintering

monarch populations had fallen steeply. In fact, during the winter of 2009-2010 the occupied area of Mexican forest decreased to less than half of what it had been the previous year and dipped below two hectares for the first time since record keeping began in the early 1990s. The link between the two trends seemed inescapable, and it pushed Pleasants and Oberhauser to publish their landmark 2012 paper arguing that Midwestern milkweed loss was killing the monarch. Oberhauser called it a “smoking gun.”

If the paper had been about any other insect, only a handful of specialist scientists might have taken note. But the monarch butterfly has a special place in the hearts of people in three North American nations. The insect's bright-orange color and large size, the gentle loops of its flight and, most of all, its spectacular migration have made the monarch a much loved celebrity.

And the story had a bad guy that the public was already primed to hate. Roundup's manufacturer, Monsanto (now part of the conglomerate Bayer), embodied many people's fears about genetic engineering and corporate control of agriculture. So the

“Nobody wanted to hear that the monarchs aren't declining, as crazy as that sounds.”

—Andrew Davis *University of Georgia*

idea that Monsanto's flagship product was killing America's flagship insect made big news. Oberhauser and Pleasants's hypothesis was widely covered by U.S. media outlets, including this one.

An army of conservationists mobilized to save the day. By 2014 more than 10,000 “monarch way stations” had sprouted around the country, thanks to a milkweed-planting program led by University of Kansas insect ecologist Orley “Chip” Taylor. In subsequent years President Barack Obama and his Mexican and Canadian counterparts all promised to protect the butterfly, and a few months later cameras clicked as the First Lady joined children as they planted milkweed in a special pollinator garden.

COUNTS THAT DIDN'T ADD UP

BUT EVEN AS THE MILKWEED limitation hypothesis gained public support, some scientists suspected it was being built on a flimsy foundation. One of the first to voice doubts was Davis, the Georgia ecologist. He had been analyzing counts of monarchs whose late-summer journeys toward Mexico took them through a handful of “funnel points”: Peninsula Point, sticking into the northern edge of Lake Michigan, and Cape May in New Jersey, a small strip of land bounded by the Atlantic Ocean and Delaware Bay. At each of these places, for several decades, volunteers have tallied south-going insects and birds at the end of summer. For monarchs, Davis noted, the numbers did not show a steady decline but bounced up and down year to year, as is typical of insect populations.

Davis's paper got scant attention when he published it in 2012, and Oberhauser and Pleasants noted that the funnel points were north and east of the corn belt, so they would not show the effects of losses in Midwestern farm fields. “Nobody wanted to hear that the monarchs aren't declining, as crazy as that sounds,” Davis says.

His paper did get the attention of Anurag Agrawal, an evolutionary ecologist at Cornell University who had studied how monarchs use chemicals produced by milkweed. He, too, began to suspect that Pleasants and Oberhauser's story, while clear and compelling, was too simple to explain the population dynamics of an insect traversing a vast and varied landscape. In Agrawal's home state of New York, for example, farm fields nestle among meadows, pastures and other ecosystems. It seemed to him that even if milkweed disappeared from crop rows, there would be plenty of other places for monarchs to find the plants.

Not everyone welcomed this perspective, Agrawal says. At a 2012 meeting that Oberhauser hosted at the University of Minnesota, he asked a group of participants what they thought of Davis's recent paper. Agrawal recalls that Chip Taylor grabbed his arm and asked him not to suggest that a monarch decline might be overstated because it would undermine conservation efforts. “I was in utter disbelief,” Agrawal says. “For somebody to get into your personal space, grab your hand and say, ‘Don't let me hear you say this’—I'll never forget it.” Taylor says he does not remember the encounter and doubts it happened.

But there were others who shared Agrawal's and Davis's doubts. Leslie Ries, an ecologist at Georgetown University, who was also at that meeting, turned to data from a monitoring program run by the North American Butterfly Association, or NABA. The group recruits volunteers to drive to selected sites and record all the butterflies they see within a 24-kilometer-diameter circle over a single day. Ries reported in a 2015 paper that their data set, as well as a separate one specific to Illinois, showed no evidence that the monarch population in the north had declined over 21 years.

Agrawal went a step further, gathering several long-term tallies of monarch populations at different parts of the life cycle, including the overwintering data, the NABA data and the funnel-point counts. He and several colleagues wanted to see whether population estimates at one stage could predict estimates at the next stage—a chain of connections crucial to the argument that fewer summer milkweed plants in the Midwest led to fewer winter butterflies in Mexico. The scientists reported in 2016 in the journal *Oikos* and again in 2018 in *Science* that there was one big gap near the end of this chain: the last end-of-summer counts did not, in fact, predict winter populations. As Ries had found, summer counts stayed roughly constant even when the winter counts fell. Agreeing with Davis, Agrawal and his co-authors suggested that something seemed to be culling monarchs during their southward fall migration, which seemed more important than events during summer breeding.

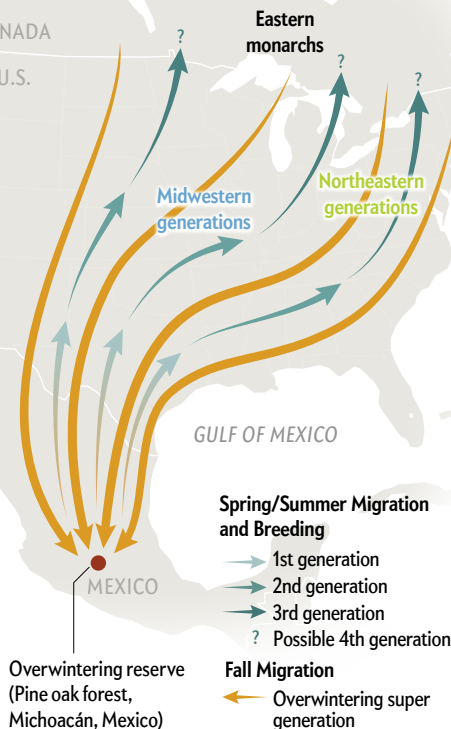
A different kind of study gave the skeptics further ammunition. In 2017 Tyler Flockhart, a population biologist then at the University of Guelph in Ontario, sought to determine not why monarchs were dying but where they were coming from. He and his colleagues analyzed isotopes of the elements hydrogen and carbon in more than 1,000 monarch butterflies collected in Mexico by Brower and others over four decades. These isotopes are present in varying ratios in different regions and are taken up by the insects' bodies and wings, forming a kind of geographic signature that indicates where the overwintering but-



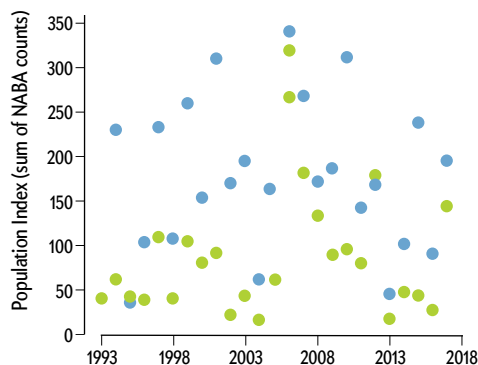
Monarch Ups and Downs

Every year millions of monarch butterflies travel from their winter home in Mexican mountains to summer breeding fields across the eastern U.S. and Canada. The winter population has dwindled in an alarming way. Scientists first blamed the herbicide-driven loss of milkweeds where butterflies lay eggs in the Midwest. But recent data show these populations go up and down, leading some ecologists to suggest the real threat is elsewhere. Others remain convinced that vanishing milkweed is the problem.

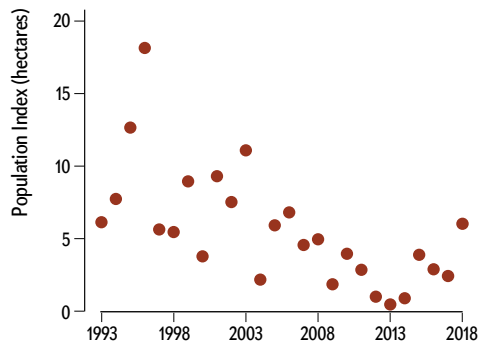
A separate group of monarch stays west of the Rocky Mountains, wintering on the California coast. That population has dropped from millions to about 30,000 recently. But because their habitat is different from the eastern monarch, scientists suspect causes of the drop are different as well.



Midwestern and Northeastern Population Sizes Fluctuate

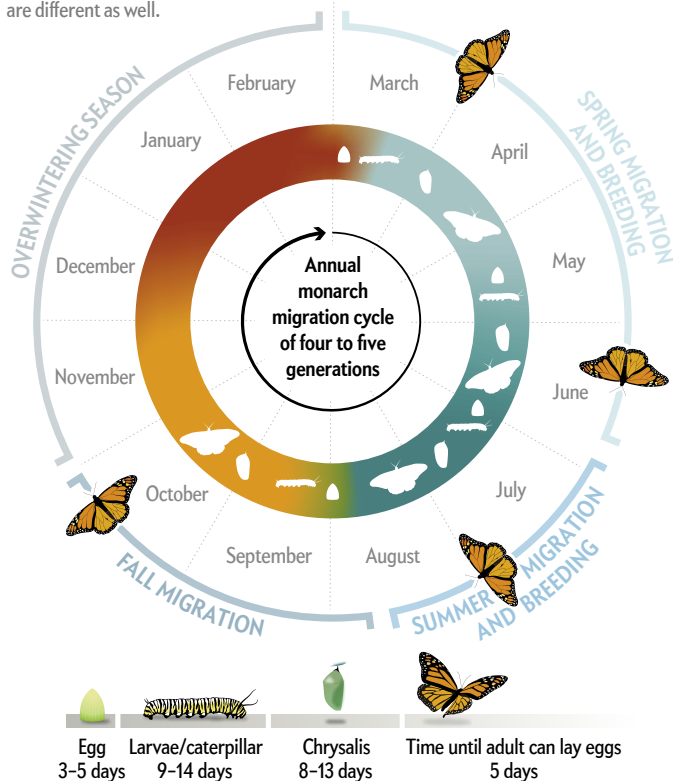


Overwintering Population Size Trends Down



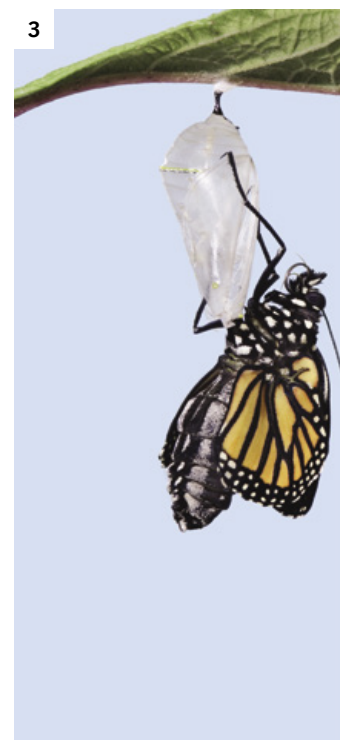
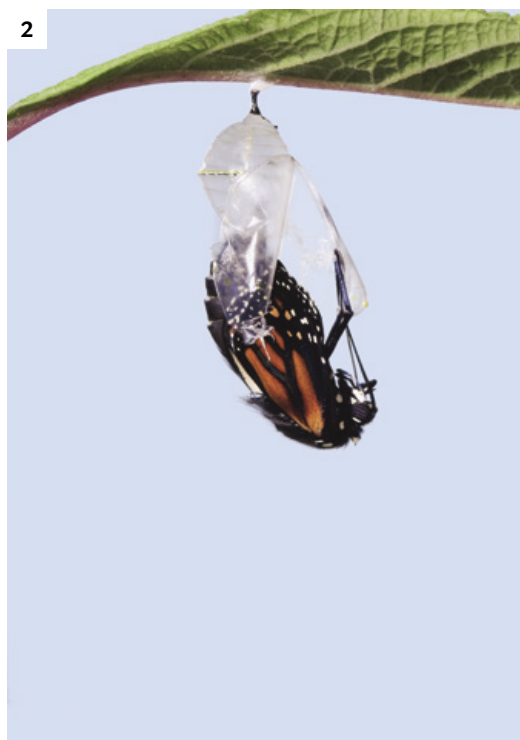
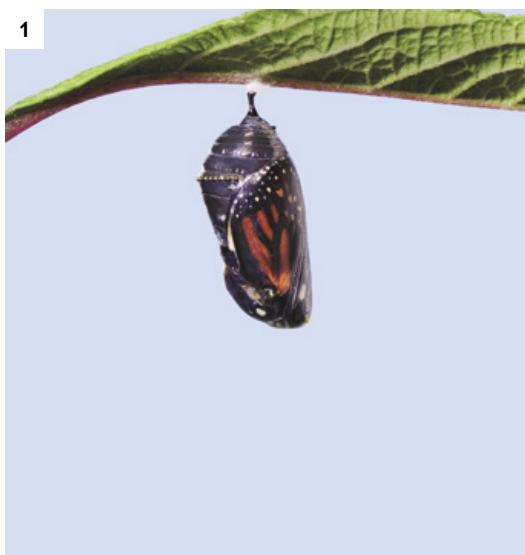
Differing Trends and Seasons

Since 1993 summer counts of monarchs in the U.S. Midwest and Northeast, calculated by Cornell University ecologist Anurag Agrawal and his colleagues, show repeated peaks and valleys. The cycles lead the scientists to believe milkweed loss has not threatened the summer butterflies. But monarch counts at their small winter home in Mexico show a downward trend. (That group has rebounded somewhat during the past three years but has not regained historical abundance.) This points to an ongoing problem—perhaps loss of forest or nectar plants—closer to the southern end of the insects' journey.



One generation lasts approximately one month, except for the overwintering super generation, which lives for up to eight months.

SOURCES: "MECHANISMS BEHIND THE MONARCH'S DECLINE," BY ANURAG A. AGRAWAL AND HIDETOSHI INAMINE, IN *SCIENCE*, VOL. 340, JUNE 2018; WORLD WILDLIFE FUND, MEXICO (2018 winter population data); JOURNEY NORTH CITIZEN SCIENCE PROJECT, UNIVERSITY OF WISCONSIN-MADISON ARBORETUM (annual cycle)



AFTER ABOUT 10 DAYS in a chrysalis an adult butterfly emerges. It strains against the thin container (1). Then the insect pulls itself out (2). Finally, the new butterfly spreads its wings (3, 4). There are four to five generations of the butterflies every year.

terfly originally fed. Flockhart concluded that the Midwest appeared to be the departure point for only around 38 percent of Mexico-bound monarchs. Monarchs also came in large numbers from the northeastern and southern U.S. and from central and eastern Canada, where corn and soybeans, on a percentage basis, cover far less land.

DIFFERENT SUSPECTS

TO AGRAWAL AND DAVIS, Flockhart had provided more damning evidence against the milkweed limitation hypothesis. If fewer than two in five monarchs come from the corn belt to begin with, they asked, how could milkweed loss there account for the dramatic losses in Mexico?

Flockhart himself is more cautious. Although there may still be enough total milkweed across North America to support a healthy monarch population, he suspects that the use of Round-up may have shifted the milkweed distribution in ways that could do harm. If the chemical's effect has been to concentrate milkweed plants in smaller areas outside farm fields, female monarchs may have to lay all their eggs closer to one another, forcing more caterpillars to compete for the same food and stressing the population, he suggests.

Flockhart's speculation highlights a quandary faced by milkweed contrarians such as Agrawal and Davis. Simply poking holes in the limitation hypothesis was not enough. They needed a different culprit to convince scientists something else was going on, and they did not really have one.

Then, in the spring of 2019, a separate team of researchers found two likely suspects: harm to nectar-producing plants along the migratory route and changes in forest density in Mexico. In a paper published in the *Proceedings of the National Academy of Sciences USA*, a team led by Elise Zipkin, a quantitative ecologist at

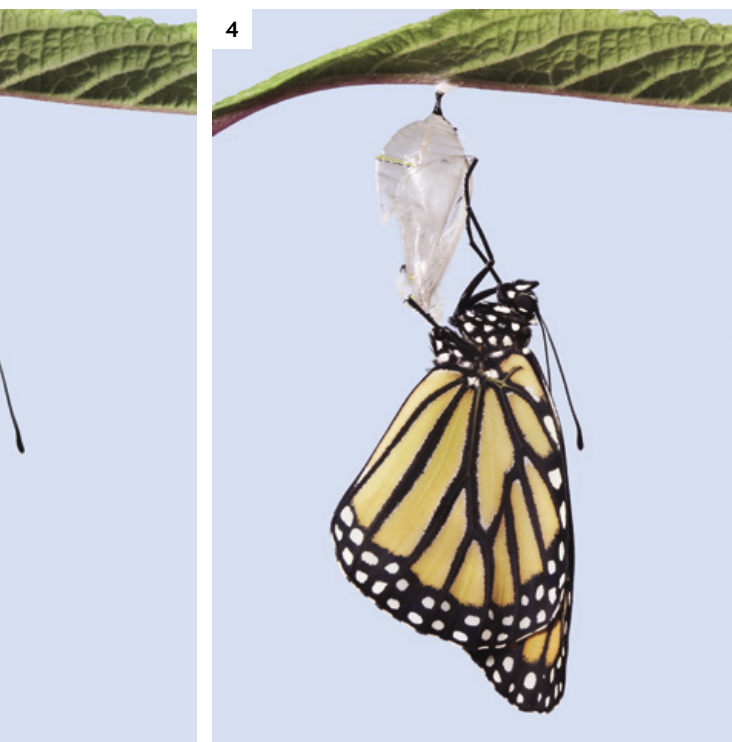
Michigan State University, examined statistical correlations among monarch population sizes at different times of the year and a vast array of environmental data. It was the first investigation to divide the winter monarchs into their 19 individual colonies rather than lumping all the forested areas together. Colonies with more dense forest cover, it turned out, hosted more butterflies. "It's shocking that nobody had done that before," Zipkin says.

Zipkin's team also used satellite imagery to quantify the amount of living plant material in a given landscape. When the southern U.S. was greener in the fall, more monarchs arrived in Mexico; when it was browner, as happens during droughts, fewer did. This pattern arose because greener, healthier plants produce more nectar capable of sustaining migrating monarchs, Zipkin and her co-authors suspect. And indeed, a powerful drought hit the southern U.S. between 2010 and 2013, just as the Mexican monarch population was bottoming out.

To Agrawal and Davis, the study pointed to real, nonmilkweed causes of population problems late in the migration. "That's the paper that addresses it most quantitatively," Agrawal says. There are also other, more vaguely outlined suspects. Davis thinks a protozoan parasite that infects monarchs could be on the rise. According to research by Davis's fellow University of Georgia ecologist Sonia Altizer (she and Davis are married), levels of *Ophryocystis elektroscirrha*, which can weaken or kill monarchs, might be reaching higher levels in insects in the southern U.S. Additionally, Davis and other researchers have suggested that habitat change has increased physiological stress in migrating monarchs, sapping their endurance during the long fall trek.

A NEW CASE

THE NEW EVIDENCE could indicate that there may be multiple culprits in the monarch decline, not just one. That perspective has



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even won over—partly—Oberhauser, the original milkweed-loss proponent. “I was probably being too strong in my argument that there was nothing happening in the migratory range,” says the scientist, now director of the University of Wisconsin–Madison Arboretum. Others have described the monarchs’ plight as “death by a thousand cuts.”

But she still believes milkweed loss is the deepest cut. “I know Andy and Anurag really well. I like both of them a lot,” Oberhauser says. “But I’m sort of tired of this argument” that something other than wipeout of milkweed plants is primarily responsible for the decimation of winter numbers. How could something capable of taking out so many monarchs in transit to Mexico remain hidden, she asks? Only milkweed availability and weather changes strongly affect monarch numbers, according to a computer model she and some colleagues used in a 2017 study.

Oberhauser and Pleasants also contend that summer counts that show no decline—numbers relied on by Agrawal, Ries and Davis—had problems: They were done by volunteers who rarely ventured into farm fields, so they missed steep population drops in those places. Logically, she insists, there have to be summer drop-offs. If monarchs’ winter populations are dwindling to lower and lower numbers year by year, how could the offspring of that shrinking group rebound to the same high summer numbers in many years? “It just makes absolutely no biological sense,” she says.

Zipkin also thinks the milkweed limitation hypothesis remains in play. Along with Oberhauser, she has found evidence in data from Illinois that glyphosate use, in conjunction with changes in springtime weather, can affect local monarch butterfly abundance in summer. “It’s hard for me to believe ... that the amount of milkweed on the landscape is not influencing monarchs. My question is: How much is it doing that?” Zipkin says.

Indeed, that is everyone’s question. To get an answer, scientists have launched a data-gathering effort called the Integrated Monarch Monitoring Program, which aims to do statistically robust counts of monarchs correlated with habitat variables in hundreds of locations across the continental U.S. Program leaders have randomly selected sites and invited both professional and citizen scientists to monitor them and send in data using standardized guidelines so researchers can look for trends. Volunteers have been collecting data since 2017, and there are now 120 people monitoring 235 sites. “We are getting some power, ramping up,” Oberhauser says.

All sides agree that helping the monarch cannot wait until the science is settled. The area of Mexican forest occupied by monarchs plummeted in 2013 to a spot barely larger than a standard soccer pitch, a record low. Although the migratory population has rebounded somewhat since then, most researchers still view its status as precarious. The U.S. Fish and Wildlife Service says it will rule on the endangered species petition later this year.

To improve butterfly-habitat regions in general, Oberhauser would like to see the U.S. Department of Agriculture increase the hectares in its Conservation Reserve Program—the most important federal program supporting wildlife areas on farmland—which has dropped to below 9.3 million from a 2007 high of almost 15 million.

Conservation measures are also needed to better protect the Mexican forests, researchers say. Even though the core forest area is officially protected—it is a United Nations World Heritage Site—logging continues on the periphery, where butterflies also spend time, and illegal avocado plantations have made incursions. A warming climate could make the reserve inhospitable to the monarch-nurturing fir trees, which require lower temperatures. Already an effort is underway to plant these trees in higher and cooler areas on the mountain slopes.

The monarch butterfly has been many things to many people: an obsession for gardeners and naturalists, a touchstone for conservationists, an international goodwill ambassador for politicians and, for much of the public, a vessel for anxieties about humans’ increasing impact on the planet. For scientists, the monarch migration began as a mystery in the 1800s, and its solution in the following century established the butterfly as a wonder of the natural world. Now the butterfly is at the center of yet another puzzle. This time its fate may depend on the answer. ■

MORE TO EXPLORE

Milkweed Loss in Agricultural Fields Because of Herbicide Use: Effect on the Monarch Butterfly Population. John M. Pleasants and Karen S. Oberhauser in *Insect Conservation and Diversity*, Vol. 6, No. 2, pages 135–144; March 2013.

Monarch Butterfly Population Decline in North America: Identifying the Threatening Processes. Wayne E. Thogmartin et al. in *Royal Society Open Science*, Vol. 4, No. 9, Article No. 170760; September 2017.

Mechanisms behind the Monarch’s Decline. Anurag A. Agrawal and Hidetoshi Inamine in *Science*, Vol. 360, pages 1294–1296; June 22, 2018.

Multiscale Seasonal Factors Drive the Size of Winter Monarch Colonies. Sarah P. Saunders et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 116, No. 17, pages 8609–8614; April 23, 2019.


FROM OUR ARCHIVES

Ecological Chemistry. Lincoln P. Brower; February 1969.

scientificamerican.com/magazine/sa



FIGURATIVE IMAGERY found in a cave in Indonesia has been dated to 43,900 years ago, which is significantly older than comparable art from Europe.

The background of the entire page is a photograph of a cave wall. On the left side, there is a large, reddish-brown painting on the rock surface. It depicts a large animal, possibly a pig or a boar, with a human figure standing next to it. The animal has a long, curved snout and is facing left. The human figure is standing upright, facing the animal. The rock surface is uneven and textured, with various shades of brown, tan, and grey. The lighting is somewhat dim, highlighting the texture of the rock and the details of the painting.

ARCHAEOLOGY

The First Story

A cave painting from Sulawesi is the oldest
known example of narrative art

By Kate Wong

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IN ROOM 67 OF THE PRADO MUSEUM IN MADRID, FRANCISCO GOYA'S *SATURN* ENTHRALLS viewers with a scene of abomination. The painting depicts the Greek myth of Cronus (Saturn in the Roman version), who ate his children for fear of being overthrown by them. Critics have interpreted Goya's rendition—the cannibal god shown wide-eyed with apparent horror, shame and madness as he devours his son—as an allegory of the ravages of war, the decay of Spanish society, the artist's declining psychological state. It is one of the great narrative artworks of all time. Vanishingly few people attain such mastery of visual storytelling, of course, but even in its lesser forms, such creative expression is special: only our species, *Homo sapiens*, is known to invent fictional tales and convey them through representational imagery.

Archaeologists have eagerly sought the origins of our distinctive artistic behavior. For a long time the oldest examples of figurative art (as opposed to abstract mark making) and depictions of fictitious creatures all came from sites in Europe dated to less than 40,000 years ago. But in recent years researchers have uncovered older instances of figurative art in Southeast Asia. Now archaeologists working on the island of Sulawesi in Indonesia have found the oldest figurative art to date. In a paper published in December in *Nature*, Maxime Aubert, Adhi Agus Oktaviana and Adam Brumm, all at Griffith University in Australia, and their colleagues report that the art—a cave painting—appears to show several fantastical human figures hunting real-life animals. If they are right, the find could also constitute the oldest pictorial record of storytelling and supernatural thinking in the world.

AN ANCIENT SCENE

THE TEAM DISCOVERED the ancient painting in 2017 in a cave known as Leang Bulu' Sipong 4 in southern Sulawesi's karst region of Maros-Pangkep, a dramatic landscape of jutting limestone towers and cliffs.

On the cave's craggy wall, six tiny hunters confront a large buffalo, brandishing ropes or spears. Nearby, other hunters set on more buffaloes, as well as pigs. The hunters appear humanlike but exhibit mysterious animal traits—one possesses a tail, for instance, and another has a beak. Such human-animal hybrids are called therianthropes (derived from the Greek words for "beast" and "human"), and they are considered to be indicators of spiritual thinking—the bull-headed minotaur of Greek mythology, for example, and the jackal-headed Egyptian god Anubis. The researchers suggest that the various figures—all rendered in a pigment with the color of old rust—are part of the same scene and that it may show a communal hunting strategy known as a game drive, in which prey are flushed from cover and driven toward hunters.

To date the images, the researchers measured the radioactive decay of uranium in mineral deposits that had formed atop them. Sampling deposits from various parts of the scene, the team obtained minimum dates ranging from 43,900 to 35,100 years ago. If the painting is at least 43,900 years old, as Aubert and his colleagues argue, it would best the previous

IN BRIEF

Homo sapiens is the only species known to make figurative art, engage in spiritual thinking and convey fictional tales through imagery.

For years the oldest traces of such creative expression came from Europe, giving rise to the idea that Europe was a "finishing school" for our kind.

A cave painting in Indonesia that is said to show a hunting scene containing supernatural elements is older than any comparable art from Europe.



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record holder for oldest figurative artwork—a 40,000-year-old painting of a cowlike animal found in a cave in Borneo—by several thousand years. It would also beat the 39,000- to 40,000-year-old *Löwenmensch* (“lion man”) figurine from Germany, which has long held pride of place as the earliest therianthrope, as well as a 17,000-year-old hunting scene from France’s famed Lascaux Cave.

The geographic location of the painting is significant. Although experts have long recognized that humans originated in Africa, “Europe was once thought of as a ‘finishing school’ for humanity,” says archaeologist April Nowell of the University of Victoria in Canada, because all the oldest known examples of art and other sophisticated behaviors were found there. But in reality, the pattern of discoveries just reflected the disproportionate amount of archaeological research that was being carried out in Europe, especially in France. “This new discovery adds to an already rich record of early and varied rock art from [Indonesia and Australia] and underscores the importance of conducting research outside Europe,” Nowell says.



CAVE PAINTING was discovered by archaeologists at a site called Leang Bulu' Sipong 4 on the Indonesian island of Sulawesi (1). The entrance to the cave, located high above the ground, is difficult to access (2).

The position of the newfound painting, in a cave whose entrance some 23 feet above the ground is hard for modern visitors to access without a ladder or climbing equipment, is also intriguing. In Europe, early cave paintings are often found in deep, pitch-dark passages that would have been difficult to get to and work in, which suggests that these places perhaps had special meaning to the artists. Brumm notes that in Sulawesi, ancient images are mostly found near the entrances to caves and rock-shelters, so they occur in the light zone, not the dark one. But as in the case of the Leang Bulu' Sipong 4 painting, they were created in high, hard-to-reach caves and niches in the region’s limestone towers and cliff faces. “Apart from the art, these sites otherwise show no evidence for human habitation, and we assume ancient people used them just for image making,” Brumm says. “Why, we don’t know. But perhaps creating cave art in such inaccessible, liminal locations high above the ground surface had some sort of deeper cultural and symbolic significance.” He adds that to reach these spots, the artists presumably had

FIGURES INTERPRETED as theri-anthropes—mythical beings that are part human, part animal—are said to hunt a small buffalo endemic to the region in one section of the cave painting (1). Although some of the imagery has worn away, a photostitched panorama of the full rock art panel (2) and a tracing of the panel (3) show additional theri-anthropic figures, along with several buffaloes as well as some wild pigs. Samples of mineral deposits that formed atop the figures were dated using uranium-series analysis, which measures the radioactive decay of uranium. The samples yielded minimum dates ranging from 43,900 to 35,100 years ago.



to climb up vines or perhaps bamboo poles—or, in some cases, pick their way through the networks of interior cave passages inside the karst towers. But although the ancient artists in Sulawesi and their counterparts in Europe may both have made their creations in places imbued with meaning and used some similar stylistic conventions in portraying their subjects, “any direct historical or cultural connection between the ice age animal art in Indonesia and Europe is unlikely,” Brumm says.

Indeed, although the newly found painting may push back the date for the earliest figurative, theri-anthropic and narrative art, it reveals little about the driving force behind the emergence of such creative expression. For decades scholars have puzzled over what seems to have been a long lag between the origin of modern human anatomy and modern human behaviors such as creating art. Whereas modern anatomy evolved hundreds of thousands of years ago, the elements of modern behavior—as re-

“One very interesting thing about humans is our enhanced working memory. It allows us to plan, sequence events in our minds before enacting them and, of course, tell stories.” —April Nowell *University of Victoria*

vealed through the material culture preserved in the archaeological record—coalesced rather later. Some have posited that a late-breaking cognitive shift might have supercharged our ancestors’ powers of ingenuity. Others suppose that cultural, social or environmental factors—or some combination thereof—stoked their creative fires. “This cave art we have dated doesn’t provide any direct insight into this interesting question—sadly!” Brumm says. But in light of the available evidence, he suspects that fictional storytelling arose long before this painting—“perhaps even before our species spread out of Africa.”

The image may also illuminate other aspects of the psyches of our predecessors. “One of the most interesting things about humans is our enhanced working memory,” Nowell explains. “It allows us to plan for the future, sequence events in our minds before enacting them and, of course, tell stories.” She notes that anthropologist Polly Wiessner of the University of Utah has shown that among many contemporary hunter-gatherers, people talk about different things depending on the time of day. During daylight hours they tend to gossip or discuss economic issues or politics. At night, in contrast, they tell stories and sing songs.

“Stories and songs are what bring people together,” Nowell remarks. “This panel suggests that this tradition of storytelling goes back [tens of] thousands of years. These stories can be about real events or mythological ones—they can instruct and entertain at the same time.” Although we will probably never know what the Sulawesi tableau was about specifically, she says, “as we collect these stories, these scenes, we begin to develop an understanding of what was meaningful to these particular people at this particular time and place.”

OPEN QUESTIONS

REGARDING WHO PAINTED the figures in Leang Bulu’ Sipong 4: No human skeletal remains have turned up in that cave or at any other site on Sulawesi from that time period. We know human species besides *H. sapiens*, including Neandertals, made art, although so far it appears to have been exclusively abstract. We also know other human species inhabited Southeast Asia in the not so distant past: *Homo floresiensis* resided on the Indonesian island of Flores 60,000 years ago, *Homo luzonensis* lived in the Philippines as recently as 50,000 years ago, and a genetic study has concluded that a late-surviving group of Denisovans may have interbred with *H. sapiens* in Indonesia or New Guinea just 15,000

years ago. Asked whether one of these other species might have painted the hunting scene, Brumm says, “Given the sophisticated nature of the imagery, our working hypothesis is that modern humans—people with essentially the same cognitive ‘architecture’ as us—made this cave art. It is presumed that these people became established in Sulawesi as part of the initial wave of migration of *Homo sapiens* into Indonesia at least 70,000 to 50,000 years ago.”

But the sophistication of the imagery is a matter of some dispute. Archaeologist Paul Pettitt of Durham University in England, an expert on early art who was not involved in the new study, points out that although one animal in the group is at least 43,900 years old, most of the other figures are not dated. “‘Scenes’ are very rare in Pleistocene art,” he observes. “If this were in Europe, Africa or North America, it would date to no more than [10,000] years ago.” Pettitt notes that the so-called therianthropes are out of scale with the animals they are said to be hunting. “Could they be unrelated to the animals?” he wonders. Or might they even have been painted at a much later time? “We know that in Europe, ‘painted caves’ were actually decorated in several phases separated by thousands of years,” he says. Geochemical analysis of the pigments involved could be used to establish confidence that the images in Leang Bulu’ Sipong 4 are contemporary.

Pettitt is also not convinced the hunters are therianthropes—or even humanlike. “Some are vague and certainly open to question,” he says. “Even the clearest examples could be quadrupeds,” he adds, remarking on the horizontal depiction of these figures. And the alleged spears are merely “long lines that just pass close to some ‘humans’—hardly weapons in hand,” he says. “So it is an open issue as to whether these represent humans and, if it is a scene, one of hunting.”

Future work may bring resolution. The discovery team’s surveys in the region have turned up many more sites containing figurative paintings that remain to be dated. Perhaps they will furnish new clues to the origins of the image-making, storytelling, myth-inventing modern human mind. ■

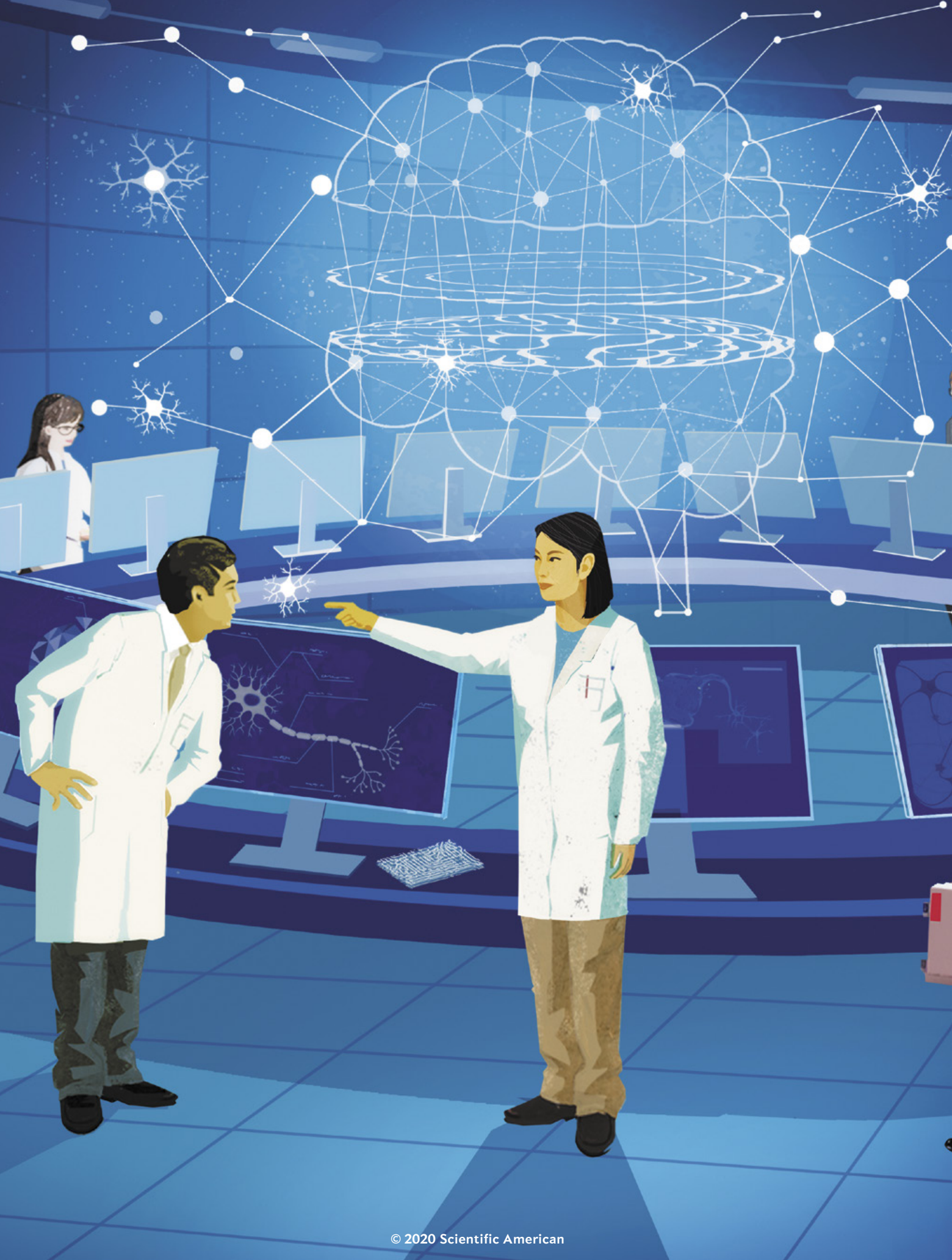
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The Brain Learns in Unexpected Ways

Neuroscientists have discovered a set of unfamiliar cellular mechanisms for making fresh memories

By R. Douglas Fields

IN BRIEF

The connecting points between neurons, called synapses, are where learning is thought to occur. Yet the synapses alone store recollections of only the most elementary reflexes.

Learning and memory require the coupling of information from many different brain regions. This activity alters the physical structure of myelin, the insulating material surrounding the wiring that connects neurons.

Myelin, it turns out, plays a key role in learning by adjusting the speed of information transmission through neural networks.

Our concepts of how the two and a half pounds of flabby flesh between our ears accomplish learning date to Ivan Pavlov's classic experiments, where he found that dogs could learn to salivate at the sound of a bell. In 1949 psychologist Donald Hebb adapted Pavlov's "associative learning rule" to explain how brain cells might acquire knowledge. Hebb proposed that when two neurons fire together, sending off impulses simultaneously, the connections between them—the synapses—grow stronger. When this happens, learning has taken place. In the dogs' case, it would mean the brain now knows that the sound of a bell is followed immediately by the presence of food. This idea gave rise to an oft-quoted axiom: "Synapses that fire together wire together."

The theory proved sound, and the molecular details of how synapses change during learning have been described in detail. But not everything we remember results from reward or punishment, and in fact, most experiences are forgotten. Even when synapses do fire together, they sometimes do not wire together. What we retain depends on our emotional response to an experience, how novel it is, where and when the event occurred, our level of attention and motivation during the event, and we process these thoughts and feelings while asleep. A narrow focus on the synapse has given us a mere stick-figure conception of how learning and the memories it engenders work.

It turns out that strengthening a synapse cannot produce a memory on its own, except for the most elementary reflexes in simple circuits. Vast changes throughout the expanse of the brain are necessary to create a coherent memory. Whether you

are recalling last night's conversation with dinner guests or using an acquired skill such as riding a bike, the activity of millions of neurons in many different regions of your brain must become linked to produce a coherent memory that interweaves emotions, sights, sounds, smells, event sequences and other stored experiences. Because learning encompasses so many elements of our experiences, it must incorporate different cellular mechanisms beyond the changes that occur in synapses. This recognition has led to a search for new ways to understand how information is transmitted, processed and stored in the brain to bring about learning. In the past 10 years neuroscientists have come to realize that the iconic "gray matter" that makes up the brain's outer surface—familiar from graphic illustrations found everywhere, from textbooks to children's cartoons—is not the only part of the organ involved in the inscription of a permanent record of facts and events for later recall and replay. It turns out that areas below the deeply folded, gray-colored surface also play a pivotal role in learning. In just the past few years a series of studies from my laboratory and others has elucidated these processes, which could point to new ways of treating psychiatric and developmental disorders that occur when learning impairments arise.

If synaptic changes alone do not suffice, what does happen inside your brain when you learn something new? Magnetic resonance imaging methods now enable researchers to see through a person's skull and examine the brain's structure. In scrutinizing MRI scans, investigators began to notice differences in the brain structure of individuals with specific highly developed skills. Musicians, for example, have thicker regions of auditory cortex than nonmusicians. At first, researchers presumed that these subtle differences must have predisposed clarinetists and pianists to excel at their given skills. But subsequent research found that learning changes the structure of the brain.

The kind of learning that leads to alterations in brain tissue is not limited to repetitive sensorimotor skills such as playing a musical instrument. Neuroscientist Bogdan Draganski, currently at the University of Lausanne in Switzerland, and his colleagues witnessed increases in the volume of gray matter in medical students' brains after they studied for an examination. Many different cellular changes could expand gray matter volume, including the birth of new neurons and of nonneuronal cells called glia. Vascular changes and the sprouting and pruning of axons and dendrites that extend from the main body of a neuron could also do the same. Remarkably, physical changes in the brain can happen much faster during learning than might be expected. Yaniv Assaf of Tel Aviv University and his colleagues showed that 16 laps around a race track in a computerized video game were enough to cause changes in new players' hippocampal brain region. Structural alterations in the hippocampus in these gamers make sense because this brain region is critical for spatial learning for navigation. In other studies, Assaf and, separately, Heidi Johansen-Berg of the University of Oxford were surprised to find changes in unexpected parts of the brain, including regions that have no neurons or synapses—areas known as white matter.

DEEP LEARNING

CONSCIOUSNESS ARISES from the cerebral cortex, the three-millimeter-thick outer layer of the human brain, so this gray matter layer is where most researchers expected to find learning-induced modifications. But below the surface layer, billions of

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tightly packed bundles of axons (nerve fibers), much like tightly wound fibers under the leather skin of a baseball, connect neurons in the gray matter into circuits.

These fiber bundles are white because the axons are coated with a fatty substance called myelin, which acts as electrical insulation and boosts the speed of transmission by 50 to 100 times. White matter injury and disease are important areas of research, but little attention has been given in these investigations until recently to a possible role of myelin in information processing and learning.

In the past 10 years studies have begun to find differences in white matter in brain scans of experts with a variety of skills, including people with high proficiency in reading and arithmetic. Expert golfers and trained jugglers also show differences in white matter compared with novices, and white matter volume has even been associated with IQ. If information processing and learning arise from the strengthening of synaptic connections between neurons in gray matter, why does learning affect the brain's subsurface cabling?

A possible answer began to emerge from cellular studies in my lab investigating how synapses—but also other brain areas—change during learning. The reason for looking beyond the synapse was that most of the drugs we have for treating neurological and psychological disorders work by altering synaptic transmission, and there is a pressing need for more effective agents. The present focus on synaptic transmission might cost us opportunities for better treatments for dementia, depression, schizophrenia or post-traumatic stress disorder (PTSD).

In the early 1990s my lab at the National Institutes of Health and others began to explore the possibility that glia might be able to sense information flowing through neural networks and alter it to improve performance. Experimental evidence that has accumulated since then shows that all types of glial cells respond to neural activity and can modify information transmission in the brain. One of the most surprising of these new findings involves myelin.

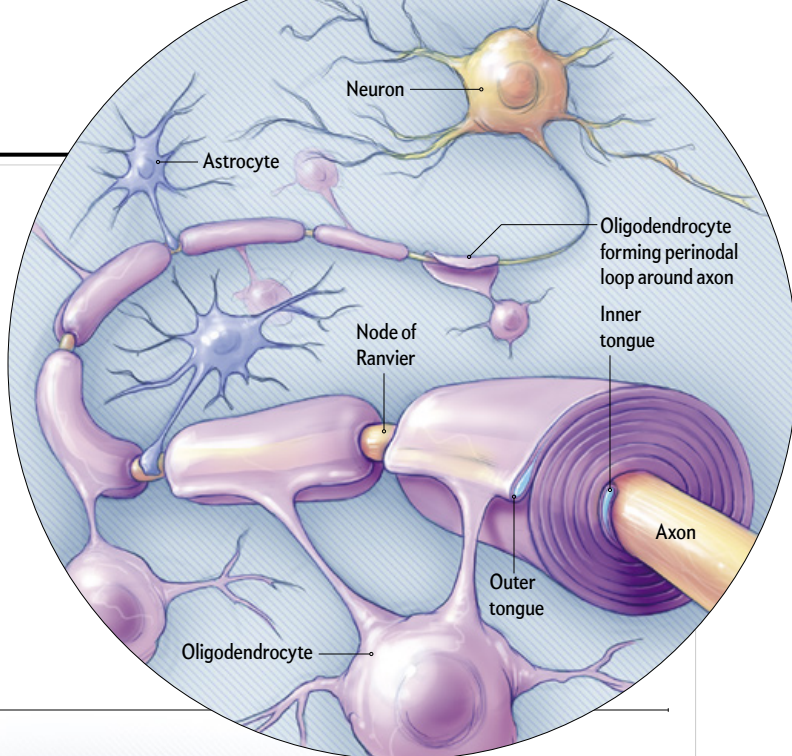
Myelin insulation is formed by layers of cell membrane wrapped around axons like electrical tape. In the brain and spinal cord, octopus-shaped glial cells (oligodendrocytes) do the wrapping. In the limbs and trunk, sausage-shaped glial cells (Schwann cells) perform the same task. Many oligodendrocytes grip an axon and wrap layers of myelin around it in segments, like the stacked hands of baseball players gripping a bat to determine which team bats first. The tiny gap between two myelin segments exposes a one-micron section of bare axon where ion channels that generate electrical impulses become concentrated. These spaces, known as the nodes of Ranvier, act like bioelectric repeaters to relay an electrical impulse from node to node down the axon. The speed of impulse transmission increases as more layers of myelin are wrapped around the axon, protecting it better against voltage loss. Also, as a node of Ranvier becomes squeezed more tightly by the adjoining myelin segments, an elec-

White Stuff Matters

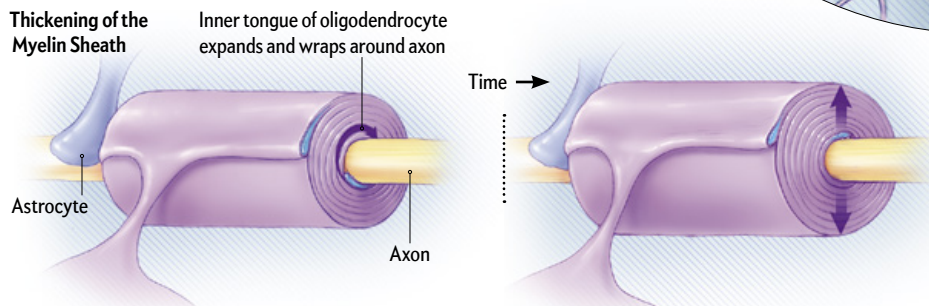
Neuroscience textbooks recount that the connecting points between neurons—the synapses—undergo alterations when learning takes place. But new research shows that changes also occur in myelin, part of the white matter that forms a sheath around the long filaments (axons) that stretch out from the cell body of a neuron.

Worker Cells

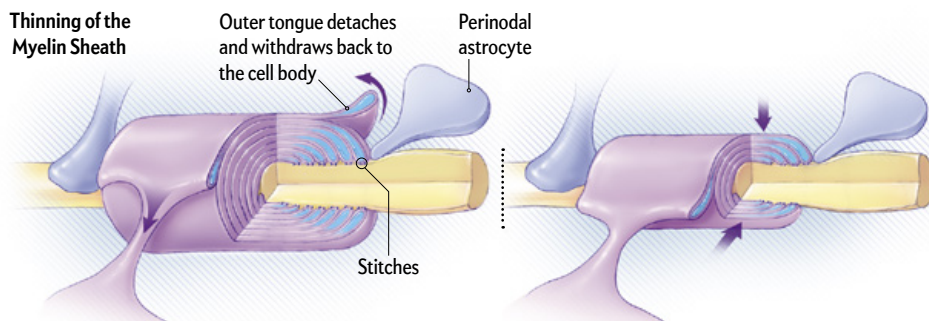
Insulating sheaths made of fatty, white myelin control the rate at which electrical signals travel along axons. Cells called oligodendrocytes loop around and wrap myelin on an axon—and, in some cases, remove it. Small gaps in myelin (nodes of Ranvier) contain ion channels that generate electrical impulses. Another cell type, the perinodal astrocyte, stops the secretion of the myelin-removing thrombin (*not shown*).



Thickening of the Myelin Sheath



Thinning of the Myelin Sheath



Wrapping and Unwrapping a Neuron

Oligodendrocytes start wrapping myelin around an axon in electrically active neurons. The degree of myelination controls how fast a signal travels along an axon, with thicker sheaths producing speedier transmissions. The enzyme thrombin cuts the stitches that bind myelin to the axon, and the perinodal astrocyte brings this process to a halt to procure the desired thickness. Varying myelin's depth ensures that dispersed signals arrive at a neural relay point at the same time, enhancing performance on a new task.

trical impulse is initiated more rapidly because it takes less time to charge the smaller amount of nodal membrane to the voltage that triggers ion channels to open and generate an impulse.

Disorders that damage myelin, such as multiple sclerosis and Guillain-Barré syndrome, can cause serious disability because neural impulse transmission fails when the insulation is damaged. But until recently, the idea that myelin might be modified routinely by neural impulses was not widely accepted. And even if myelin structure changed, how and why would this improve performance and learning?

The explanation was hiding in plain sight. It loops back to the old maxim about neurons firing and wiring together. In any complex information or transportation network, the time of arrival at network relay points is critical—think of missing a connection because your flight arrives too late.

How, then, does the transmission speed in every link in the

human brain get timed appropriately so that an impulse arrives just when needed? We know that electrical signals shuffle along at the pace of a slow walk in some axons but blaze away at the speed of a race car in others. Signals from two axons that converge on neurons that act as relay points will not arrive together unless the travel time from their input source is optimized to compensate for differences in the lengths of the two axons and the speed at which impulses travel along each link.

Because myelin is the most effective means of speeding impulse transmission, axon myelination promotes optimal information transmission through a network. If oligodendrocytes sense and respond to the information traffic flowing through neural circuits, then myelin formation and the way it adjusts impulse-transmission speed could be controlled by feedback from the axon. But how can myelinating glia detect neural impulses flowing through axons?

SIGNAL TRANSMISSION

OVER THE PAST 20 YEARS our research and that of other labs has succeeded in identifying many neurotransmitters and other signaling molecules that convey to glia the presence of electrical activity in the axon to stimulate myelination. Our experiments have shown that when a neuron fires, neurotransmitters are released not only at synapses but also all along the axon. We found that the “tentacles” of the octopuslike oligodendrocytes probe bare sections of axons in search of neurotransmitters being released from axons firing. When a single tentacle touches an axon that is firing, it forms a “spot weld” contact, which enables communication between the axon and the oligodendrocyte. The oligodendrocyte begins to synthesize myelin at that spot and wrap it around the axon.

When we gave oligodendrocytes in cell culture the choice of myelinating electrically active axons or ones treated with botulinum toxin to prevent the release of neurotransmitters, the oligodendrocytes opted for the electrically active axons over the silent ones by a factor of eight to one. So it may be that as a person learns to play “Für Elise” on the piano, bare axons are wrapped with myelin or the volume of existing sheaths is increased in circuits that are activated repetitively during practice, which speeds information flow through brain networks. New myelin then shows up on an MRI as changes in white matter tracts in parts of the brain that are necessary for musical performance.

Several labs have recently verified that action potentials, signals coursing the length of axons, stimulate myelination of these exposed areas of neural wiring. In 2014 Michelle Monje’s lab at Stanford University showed that optogenetic stimulation (using lasers to make neurons fire) increased myelination in the mouse brain. That same year William Richardson’s lab at University College London demonstrated that when the formation of new myelin is prevented, mice are slower to learn how to run on a wheel with some of its rungs removed. In studies where they used a confocal microscope to watch myelin form in live zebra fish, researchers in David Lyons’s lab at the University of Edinburgh and in Bruce Appel’s lab at the University of Colorado Denver observed that when the release of small sacs containing neurotransmitters from axons is inhibited, often the first few wraps of myelin slip off, and the oligodendrocyte aborts the entire process.

Recently, working with our colleagues, including Daisuke Kato and others from various institutions in Japan, we showed how myelin promotes learning by ensuring that various spiking electrical signals traveling along axons arrive at the same time in the motor cortex, the brain region that controls movement. Using genetically modified mice with impaired myelination that had been trained to pull a lever to receive a reward, we found that learning this task increased myelination in the motor cortex.

By using electrodes to record neural impulses, we found that action potentials were less synchronized in the motor cortices of mice with faulty myelination. We then boosted the synchronization of spike arrivals in the motor cortex by using optogenetics to make neurons fire at the appropriate time. The mice with impaired myelination then performed the learned task proficiently. Eventu-

ally less invasive forms of brain stimulation may become effective therapy to treat neurological and psychological disorders caused by disrupted myelination.

Despite these recent advances, stimulation to increase axon myelination is not always enough to enable new learning, because we cannot synchronize the arrival of spikes at critical relay points in neural networks simply by making the impulses travel as rapidly as possible. There must also be a way to slow the speed of impulses from inputs that arrive at those points too soon.

The myelin that has already formed on axons has to be thickened or thinned in a controlled way to speed or slow signal transmission. Prior to our findings, there was no known explanation for how the myelin sheath could be thinned to slow signals, aside from disease damage. Our latest research reveals another type of glial cell involved in these “plastic” nervous system changes.

Surrounding the node of Ranvier is a glial cell called an astrocyte. Astrocytes have many functions, but most neuroscientists have largely ignored them because they do not communicate with

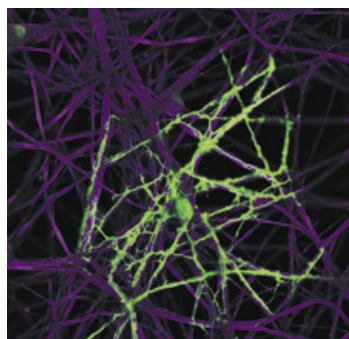
other cells through electrical impulses. Surprisingly, research in the past decade has shown that astrocytes positioned close to the synapse between two neurons can regulate synaptic transmission during learning by releasing or taking up neurotransmitters there. But until recently, myelin biologists tended to ignore the unique type of astrocyte that contacts an axon at a node of Ranvier.

What exactly do these so-called perinodal astrocytes do to thin the myelin sheath? Just as one would begin when remodeling a garment, these cells assist in cutting the “seams.” The myelin sheath is attached to the axon by a spiral junction flanking the node of Ranvier. Under an electron microscope these junctions appear

as spirals of stitches between the axon and the myelin, and the threads that form each stitch are composed of a complex of three cell adhesion molecules. Our analysis of the molecular composition of these stitch points showed that one of these molecules, neurofascin 155, has a site that can be cleaved by a specific enzyme, thrombin, to thin the myelin.

Thrombin is made by neurons, but it also can enter the brain from the vascular system. As the myelin lifts off the axon, the amount of bare axon at the node of Ranvier increases. The outer layer of myelin is attached to the axon adjacent to the perinodal astrocytes. When the myelin is detached from the axon, the outer layer withdraws into an oligodendrocyte, thinning the sheath. Both widening of the nodal gap and thinning of the myelin sheath slow the speed of impulse transmission.

We found that the enzyme’s snipping of these threads that stitch myelin to the axon can be controlled by the perinodal astrocyte’s release of an inhibitor of thrombin. We carried out experiments on genetically modified mice in which astrocytes released less of this thrombin inhibitor. When we looked at their neurons with an electron microscope, we could see that the myelin had thinned and that the nodal gap had increased. By using electronic amplifiers to detect neural impulses and measure their speed of transmission, we found that after the myelin thickness decreased



OLIGODENDROCYTE (green)
prepares to coat an axon (purple)
with myelin.

in this way, the speed of impulse transmission in the optic nerve slowed by about 20 percent and the animals' vision declined. We were able to reverse all these changes by injecting thrombin inhibitors, which are approved for treating vascular disorders.

Our experiments support a new hypothesis: the myelin sheath's changes in thickness represent a new form of nervous system plasticity governed by the addition and subtraction of myelin. Additional layers of myelin are not added to axons as one would wrap tape around a wire, because this would tie the legs of the oligodendrocytes in knots. Instead new insulation is affixed through the construction of a new inner layer that spirals around the axon like a snake below the overlying myelin. Meanwhile the outer layer of myelin can be detached by the perinodal astrocyte to thin the sheath. The thickness of the myelin sheath is not fixed; instead it reflects a dynamic balance between the addition of layers next to the axon and removal of the outer layer under control of the astrocyte.

BRAINY WAVES

THE OPTIMAL TIMING of action potentials at relay points is critical for strengthening synapses by adjusting their timing to allow them to fire together. But myelin plasticity can contribute to neural circuit function and learning in another way—by tuning the frequency of brain-wave oscillations. Not all neural activity in the brain arises from sensory inputs. Much of it takes place because of what goes on in the brain itself at both conscious and unconscious levels. This self-generated activity consists of oscillating waves of different frequencies that sweep through the brain, just as the vibration of a car engine at a certain speed will set different parts of the automobile rattling together at resonant frequencies.

These brain waves, or oscillations, are believed to be a key mechanism for coupling neurons across distant regions of the brain, which may be important for sorting and transmitting neural information. Oscillations, for example, tie together neural activity in the prefrontal cortex, which provides contextual meaning, and in the hippocampus (responsible for encoding spatial information). This oscillatory coupling enables a person to quickly recognize a familiar face at work, but it also makes it more difficult to identify the same co-worker in an unfamiliar place.

More important, the various stages of sleep, critical for storing long-term memories, can be identified by brain waves oscillating at different frequencies. Our experiences accumulated during the day are replayed during sleep and sorted for storage or deletion based on how they relate to other memories and emotions, which can mark them as potentially useful (or not) in the future. Appropriate brain-wave oscillations are believed to be pivotal in this process of memory consolidation. But the speed of impulse transmission is critical in synchronizing brain waves.

Just as two toddlers must precisely time their leg movements to drive the up-and-down motion of a teeter-totter, the transmission delays between two populations of oscillating neurons must be timed so that coupled neurons oscillate in synchrony across long distances in the brain. Myelin plasticity is important for brain waves because the proper conduction velocity is necessary to sustain oscillations that couple two regions of the brain at the same frequency.

This conclusion is based on mathematical modeling of the fundamental physics of wave propagation done by me, together with my NIH colleagues Sinisa Pajevic and Peter Basser. In 2020 a study

by Patrick Steadman and his colleagues in Paul Frankland's lab at the University of Toronto provided convincing experimental support for the idea. Using genetically modified mice in which myelination could be temporarily halted, the researchers found that the ability to learn to fear an unsafe environment and to remember safe locations depends on the formation of new myelin. Moreover, they found that in this type of learning, brain-wave activity during sleep becomes coupled between the hippocampus and the prefrontal cortex. The prevention of new myelin formation also weakened connections and resulted in a type of impaired recall often found in people who have difficulty associating fear after a traumatic event with the appropriate context.

Learning and performing any complex task involves the coordinated operation of many different neurons in diverse brain regions and requires that signals proceed through large neural networks at an optimal speed. The myelin sheath is crucial for optimal transmission, but people begin to lose myelin in the cerebral cortex in their senior years. This gradual degradation is one of the reasons for cognitive slowing and the increasing difficulty of learning new things as we age.

Consider how transmission delays disrupt long-distance communication by telephone. Similarly, lags in the brain can cause cognitive difficulties and disorganized thinking in individuals with psychological disorders such as schizophrenia. Indeed, differences in brain-wave oscillations are seen in many neurological and psychiatric disorders. Alzheimer's disease, for instance, is associated with changes in white matter.

Drugs that control myelin production could provide new approaches to treating these problems. Because myelination is influenced by many forms of neural activity, a number of techniques—for example, cognitive training, neurofeedback and physical therapy—may be helpful in treating age-related cognitive decline and other disorders. A recent study of older adults by Jung-Hae Youn and his colleagues in South Korea indicated that 10 weeks of memory-training exercises increased recall. Brain imaging before and after training revealed increased integrity of white matter tracts connecting to the frontal lobe in the group of seniors who undertook the memory-training sessions.

These novel concepts have begun to change the way we think about how the brain works as a system. Myelin, long considered inert insulation on axons, is now seen as making a contribution to learning by controlling the speed at which signals travel along neural wiring. In venturing beyond the synapse, we are beginning to fill out the stick-figure skeleton of synaptic plasticity to create a fuller picture of what happens in our brain when we learn. ■

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Michael Wyssesson, Ph.D.

Michael Wyssesson, Professor of Geophysics and the Executive Director of the Center for Teaching and Learning at Washington University in St. Louis, is a leader in the areas of seismology and geophysical education. He has authored or co-authored

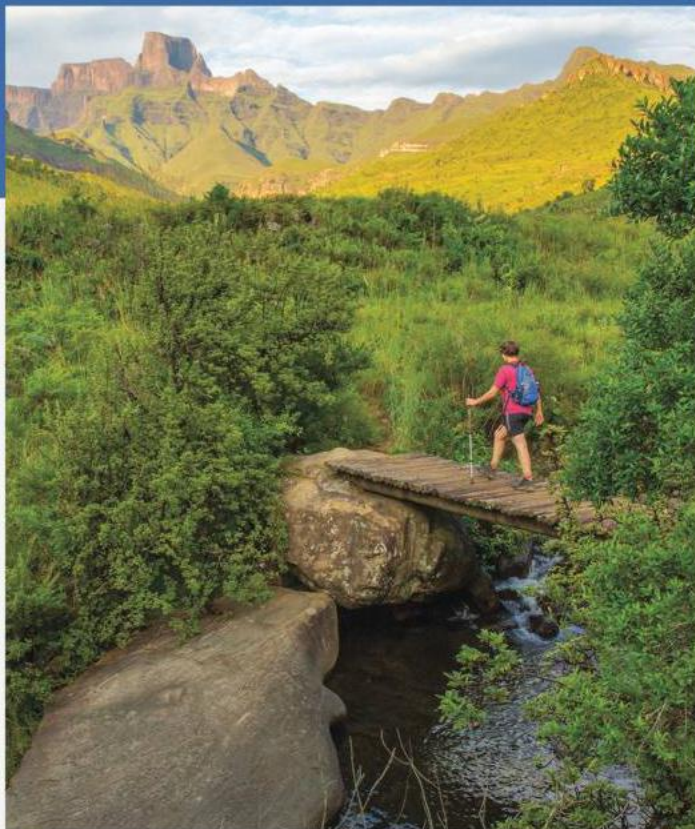
over 100 papers and reports in geophysics and science education, and over 30 textbooks ranging from grade school to graduate school. Wyssesson was Chair of the NSF's Earth Science Literacy Initiative, Chair of Earth and Space Science for the National Academy of Science report A Framework for K-12 Science Education and one of the lead architects of the new national K-12 Next Generation Science Standards.

GEOLOGY:

- Pandemics
- Civilization Exists by Geologic Consent
- How Your Grandkids Will Save the World
- The Future of Energy Resources

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Five-Night Pre- and/or Post-Cruise: Optional Expeditions

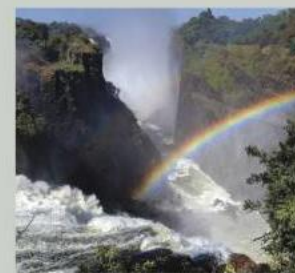
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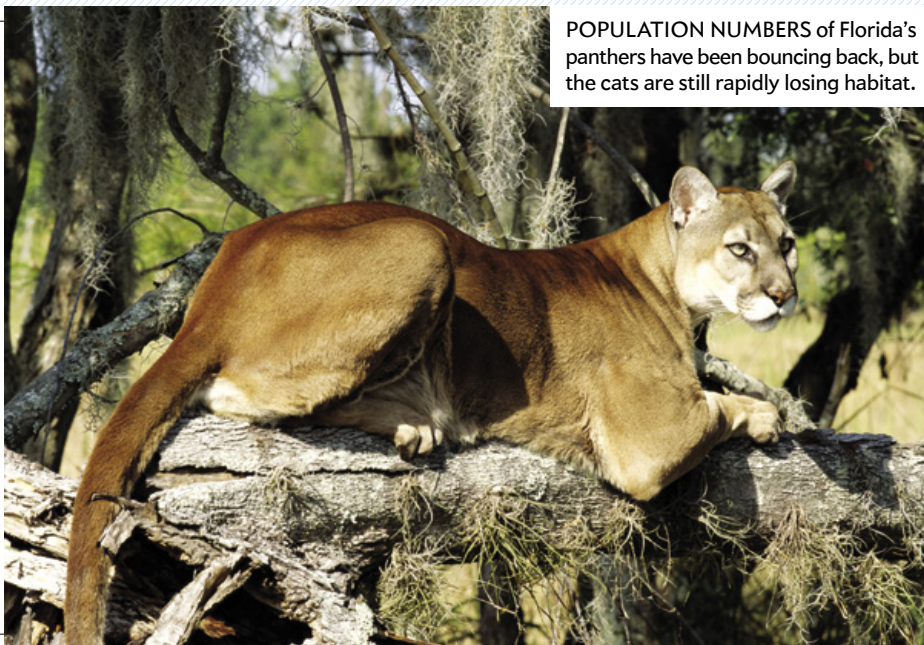
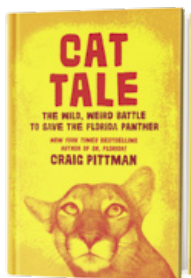
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RECOMMENDED

By Andrea Gawrylewski

Cat Tale: The Wild, Weird Battle to Save the Florida Panther

by Craig Pittman.
Hanover Square Press,
2020 (\$27.99)



POPULATION NUMBERS of Florida's panthers have been bouncing back, but the cats are still rapidly losing habitat.

Florida once came very close to losing its state animal. By the 1980s decades of hunting and rapid development had pushed the Florida panther—the only subspecies of the North American cougar found east of the Mississippi River—perilously close to extinction. With a genial wit, journalist Pittman chronicles the extended saga of a few of the dedicated scientists who fought to bring these elusive and majestic animals back from the brink. The story is replete with interpersonal drama, lucky breaks, frustrating setbacks and bureaucratic decisions based on spurious science. Pittman's tale would seem to have a happy ending: Florida's panthers have experienced a remarkable baby boom thanks to a controversial breeding program. But the big cat is not out of the woods yet—it continues to lose habitat in a state where construction is often prioritized over conservation.

—Andrea Thompson

The Scientist and the Spy: A True Story of China, the FBI, and Industrial Espionage

by Mara Hvistendahl. Riverhead Books, 2020 (\$28)



This story of international espionage begins in the unlikelyst of places—a cornfield in Iowa. In 2011 police caught three Chinese men trespassing on a farm that was partly under contract with agricultural giant Monsanto. The men were planning to dig up proprietary seeds to send back to China for reverse engineering—a scheme that, if successful, could have allowed China to reap huge profits from illegally duplicating Monsanto's seed lines. Through skillful reporting, journalist Hvistendahl details the dramatic FBI investigation that followed, ultimately uncovering far more than corn-seed theft: a U.S. federal counterintelligence program intended to protect intellectual property that racially profiled and spied on ethnic Chinese scientists and students living and working in the States.

—Sunya Bhutta

How We Learn: Why Brains Learn Better Than Any Machine ... for Now

by Stanislas Dehaene. Viking, 2020 (\$28)



The act of learning, cognitive psychologist Dehaene explains, is the construction of internal models of the outside world. Today the state of the art in artificial intelligence still pales against the powers of abstraction possessed by the human brain. For example, we—unlike most AI—can recognize a “chair” whether it has four legs or one or is made of metal or plastic. In this enlightening examination of the brain's power to learn, Dehaene dispenses with the idea that the human brain is a tabula rasa, or blank slate, arguing that it comes preprogrammed by evolution. Babies are then like “budding scientists,” making hypotheses and gathering evidence to confirm or discard them. Such insights inform Dehaene's proposed four “pillars” of learning, conditions that, if met, may maximize a human's—or a machine's—absorption of knowledge.

—Tanya Lewis

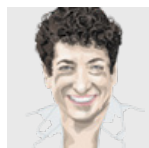
What Stars Are Made of: The Life of Cecilia Payne-Gaposchkin

by Donovan Moore.
Harvard University Press, 2020 (\$29.95)



Overturing scientific dogma is no easy thing—especially as a marginalized minority. But that is just what Cecilia Payne-Gaposchkin did in the male-dominated field of early 20th-century astronomy, as detailed in this biography by journalist Moore. Growing up in London, Payne-Gaposchkin trained at the prestigious Cavendish Laboratory before finally landing at the Harvard College Observatory. There she analyzed spectral lines from stars for her 1925 doctoral thesis entitled “Stellar Atmospheres.” Defying preexisting theories, which held that stars' compositions would mirror that of Earth's crust, Payne-Gaposchkin's studies showed hydrogen and helium to be their main ingredients. Though initially dismissed by some of her prominent male peers, her work was ultimately recognized as “the most brilliant Ph.D. thesis ever written in astronomy.”

JH PETE CARMICHAEL Getty Images



Naomi Oreskes is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *Discerning Experts* (University of Chicago, 2019).

Boring but Crucial

Instrument calibration is essential
for science—and justice

By Naomi Oreskes

One of the challenges of writing about science is that important concepts are not always exciting, and it is no small feat to make a dull subject shine. Recent events, however, have highlighted a topic that is both deadly dull and deadly serious: instrument calibration.

Calibration is the process of making sure an instrument is working accurately. Usually this involves testing against a known standard (or set of standards). Every scientist who works with an instrument learns to calibrate it; organizations that make many measurements, such as the U.S. Geological Survey, have protocols for ensuring that it is done regularly and accurately. Calibration services are a major part of the work of the National Institute of Standards and Technology, on which both industry and other federal agencies rely.

But it is not something that you do once and forget about; instruments drift, so they have to be checked regularly. Without calibration, the measurements we make may be meaningless. And this, it turns out, is what has happened with a highly consequen-

tial instrument used every day across America: the Breathalyzer, used to determine whether a driver has had too much to drink.

In 2017 a Massachusetts judge threw out thousands of drunk-driving convictions on the grounds that the kind of Breathalyzer used was not reliable. This ruling followed an earlier agreement among the state's district attorneys and lawyers representing alleged drunk drivers that data from breath tests would not be used at trial (except for serious offenses), after evidence emerged that the results were questionable. By one account, the decision affected 35,000 outstanding cases from 2011 to 2017. Another account suggests that the total number of affected cases could exceed 58,000. Other states have also questioned convictions based on Breathalyzer results: in New Jersey more than 20,000 drunk-driving convictions have been called into question.

Drunk driving is a huge problem. Every year more than a million Americans are arrested for it and, according to the Centers for Disease Control and Prevention, more than 10,000 deaths can be attributed to it. Society has a compelling interest in identifying drunk drivers and getting them off the road. But if the tools used to identify them are unreliable, then innocent people can lose their licenses and, in some cases, be wrongly convicted and incarcerated. The reverse is also true: with tens of thousands of cases where police had reason to suspect that the driver was impaired now thrown out, it is likely that many guilty parties will go free.

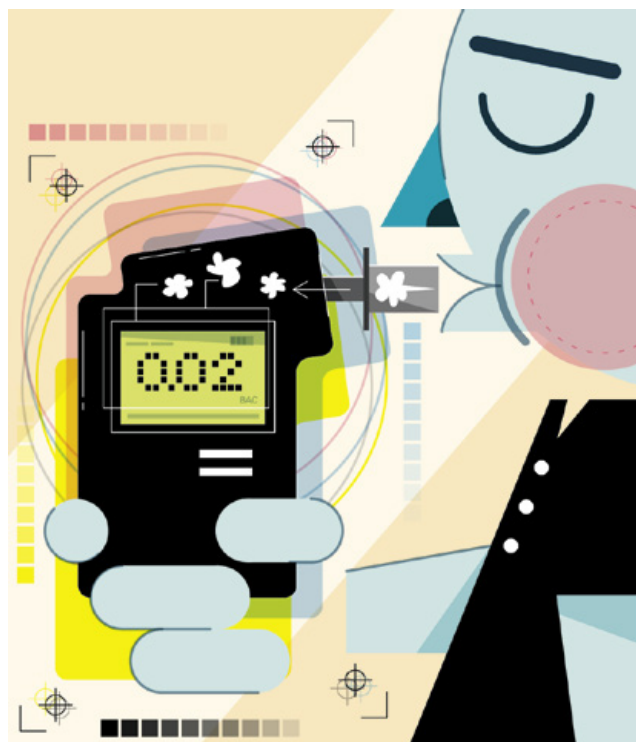
Why did this happen? One pervasive problem is instrument calibration. It turns out the Breathalyzer, like all scientific instruments, needs to be regularly calibrated, and police officers often are neither trained nor equipped to do this work. In some cases, it appears that police precincts did not even realize calibration was needed. Here is a pretty simple solution: police need to bring in technicians to check their instruments. As one company that offers instrument calibration puts it, just as motor vehicles require regular maintenance, so do the Breathalyzers used to test their drivers. It would add a bit to policing costs, of course, but surely that outcome is preferable to losing years of prosecutorial work or to sending innocent people to jail while guilty parties walk free.

There is a deeper lesson here about science and technology: scientific instruments do not perform magic tricks. You cannot just blow air in a machine and get a good result; accurate data are the product of sustained attention. It takes good work to get good numbers. For decades science teachers have been admonished to teach not just facts but processes, including the process of doing scientific research. I recall my own children raising tomatoes, performing a census of marine life and constructing volcano simulations. But what state science standards include a unit on calibration? Maybe it is time they add one.

The miscarriage of justice caused by the misuse of scientific instruments underscores why we need to understand not just the findings of science but also the processes by which scientific evidence is obtained, as boring as they seem. ■

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Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 36 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.



Physician, Brake Thyself

Doctors' driving differs by discipline

By Steve Mirsky

Medical doctors can have the letters “MD” on their cars’ license plates, which in some places can help them bend the rules regarding parking and speeding in emergencies. But if you’re at all like me—and for the sake of your loved ones, let’s hope you’re not—you have one of three highly prejudicial and unfair reactions when you see a car with MD license plates. For a fancy vehicle: Ooh, look at Mr. Big Shot driving a six-figure car. For a piece of junk: What kind of crummy doctor drives that piece of junk? For any other auto: “Emergency” my butt; you’re probably my dermatologist. (By the way, none of these opinions are in effect if the doctor is rushing to care for me.)

A logical follow-up question to the physician license-plate issue then is, Does a dermatologist drive differently than a surgeon? Finally, we have an actual scientific study to answer that vital question ... vital signs question ... vital road-signs question ... yeah, that’s it.

Anyway, the research, written up with the title “The Need for Speed: Observational Study of Physician Driving Behaviors,” is

in the 2019 edition of the notorious Christmas issue of the *BMJ*, formerly called the *British Medical Journal*, even more formerly called the *Provincial Medical and Surgical Journal* upon its founding in 1840—and perhaps informally once called *Gathering Around to See What Nigel Found While Digging Up Cadavers Weekly*.

Back to the *BMJ* article. The objective of the study was “to determine whether fast driving, luxury car ownership, and leniency by police officers differ across medical specialties.” At this point, I must note that the research was based on records of speeding tickets issued to almost 5,400 doctors who received some 15,000 tickets between 2004 and 2017 in the state of Florida. So take the location into account when considering these findings, because as I noted in the January issue while discussing rodents that were taught to drive tiny cars for science, “Video of the vehicular vermin can be found online, and, frankly, I’ve seen worse driving in Florida shopping center parking lots.”

The online article has a fun interactive feature that allows one to look at which specialists drive the fastest on average, get the most tickets for extreme speed (more than 20 miles per hour over the speed limit) and drive the most expensive cars, among other auto doc data. Given that you are clearly not looking at that interactive feature at the moment, I’ll summarize. But first: What’s an orthopod?

The online medical encyclopedia Gomerpedia defines “orthopod” thusly: “Often confused with an arthropod, an orthopod is a vertebrate animal with an endoskeleton that cares deeply about every [*sic*] else’s bones.” (“Gomer,” as is well known in the medical community, is an acronym for “get out of my emergency room,” as per the novel *The House of God*, by Samuel Shem, published in 1978.) And orthopods, also called orthopedists, are the fastest drivers. They are followed by psychiatrists. Paranoid orthopods only think they’re being followed by psychiatrists.

When it comes to getting caught driving more than 20 miles an hour over the limit, psychiatrists follow no one—they lead the pack. Second place in that category goes to general surgeons, who may reasonably be in a hurry to get to a patient in extremis. The rushing psychiatrists may simply be trying to get ahead of cardiologists, who have the priciest cars.

All of which reminds me: my father really did have a cardiologist who drove a Maserati. And that cardiologist was a woman. Which brings to mind another article in the same Christmas issue of the *BMJ*, entitled “Time’s Up for *He* and *Him* as the Default Pronouns for Doctors.” According to that piece, “most doctors are or will be women—our language should reflect that reality.”

So please revise my catty earlier remark about doctors who drive expensive cars so that it pertains to both Mr. and Ms. Big Shot. Better yet, just call them all “Doctor.” ■

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MARCH

1970 Lunar Laser Reflector

"In July of last year the astronauts of *Apollo 11* placed on the surface of the moon an array of prism-like reflectors that has made it possible to measure the distance between the earth and the moon with an accuracy approaching six inches. The important quantity, however, is not the absolute distance between the earth and the moon but the variations in distance measured over a period of months and years. Such variations can be studied to answer important scientific questions, such as how the mass inside the moon is distributed, the rate at which the continents on the earth are drifting toward (or away from) one another and changes in the location of the earth's North Pole (which shifts in response to unknown forces). A more fundamental question than any of these is whether the gravitational constant is indeed constant or whether it may slowly be weakening with the passage of time."

1920 Calling Mars

"The recent suggestion that the Martians are trying to send wireless signals to us may prove groundless, but it has at least called public attention to an important subject. The idea of exchanging thoughts with intelli-



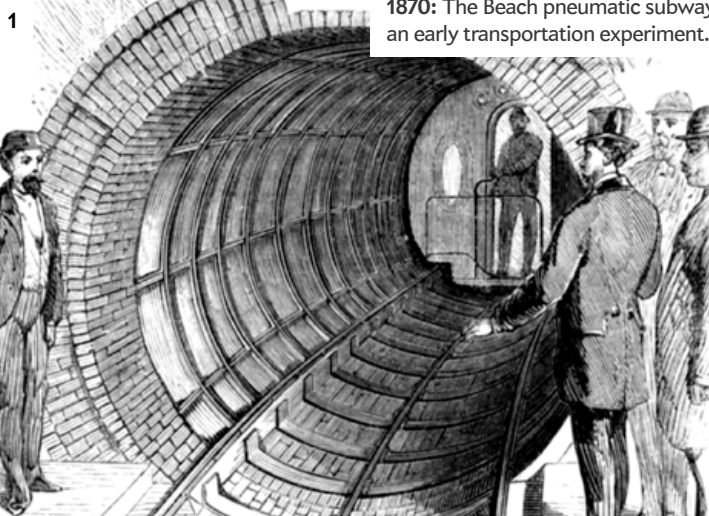
1970



1920



1870



1870: The Beach pneumatic subway, an early transportation experiment.

gent beings on another planet is too alluring for the human imagination to resist. To bring the public to the necessary point of enthusiasm, they must be assured that an exchange of signals will rapidly develop into an exchange of ideas on any and all subjects of common interest. We want to talk over our scientific, social and religious notions with the Martians, and if they have a civilization far older than ours we want to learn from them truths that will help us in our own difficulties."

1870 Pneumatic Subway

"The doors of the Beach Pneumatic Transit Company were thrown open

to the public for the first time when an 'Under Broadway Reception' was given, by special invitation to the State authorities, city officials, and members of the press. All the prominent personages of the city and State were present, and the inspection of the works gave the greatest satisfaction. The various daily newspapers have published long accounts of the event, which has produced quite a novel sensation in the metropolis. The *New York Herald* says 'it was virtually the opening day of the first underground railway in America.'

This demonstration project was designed and built by Alfred Ely Beach, then editor of this magazine.

EPIC TALES



2

CELEBRATING
175
YEARS

People Movers

Cities are well served by extensive transportation networks that move people and goods into, out of and around urban conglomerations on a daily—or hourly—basis. But there is a question of how to power these people movers. The London Underground, opened in 1863, had coal-fired steam engines pulling gas-lit cars along "tube" tunnels. It must have been spectacularly grimy. San Francisco's cable cars grab hold of moving cables under the street, which are powered by static engines. Alfred Ely Beach, an early editor in chief here, demonstrated an underground railcar puffed along by air pressure in 1870 (1). Entrepreneur Elon Musk's proposed Hyperloop plans to zip railcars through a near vacuum inside a tube. As networks of rails over and under the ground expanded with cities, they were melded with electric power grids (2) to create faster and cleaner urban transit systems. These networks now serve hundreds of millions of riders a day worldwide, and their efficiency may help mitigate climate change as populations grow. —D.S.

1915: Workers install overhead electric power lines for suburban commuter trains in Philadelphia.

Carbon Taxes Boost Jobs

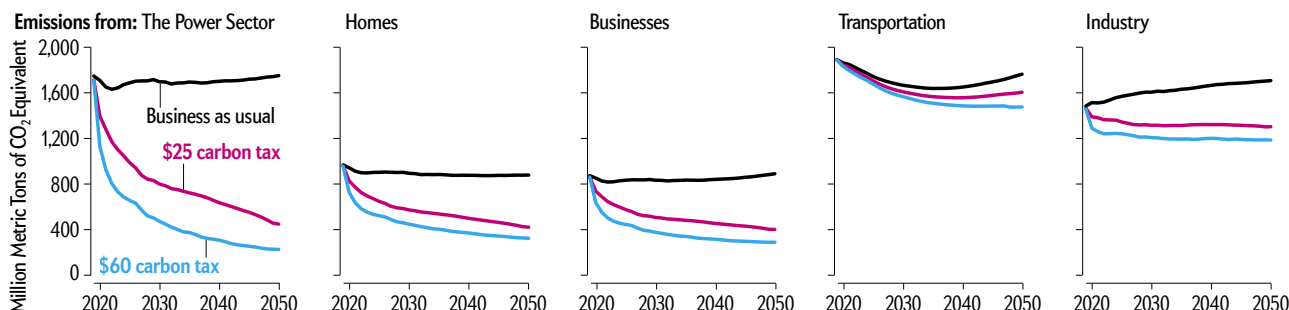
Construction and manufacturing careers would rise nationwide

Pundits have argued over whether a carbon tax would create or kill jobs ever since the U.S. Green Party first floated the Green New Deal, a plan to build a sustainable, environmentally clean economy. In the past three years a number of U.S. legislators—and Democratic presidential candidates—have released carbon-tax plans or bills, with widely varying estimates about impacts on jobs. Marilyn A. Brown and Majid Ahmadi of the Georgia Institute of Technology put the Green New Deal's details into

the U.S. Energy Information Administration's National Energy Modeling System to assess what would happen. They evaluated a \$25 and \$60 tax on each metric ton of carbon dioxide emitted by the U.S. energy system. Both scenarios would cut emissions greatly, largely by pushing up the price of fossil fuels, thereby encouraging industries and consumers to use cleaner energy sources and improve energy efficiency. Perhaps unexpectedly, the \$25 tax would create more jobs than the \$60 tax would.

Carbon Dioxide Emissions Go Down

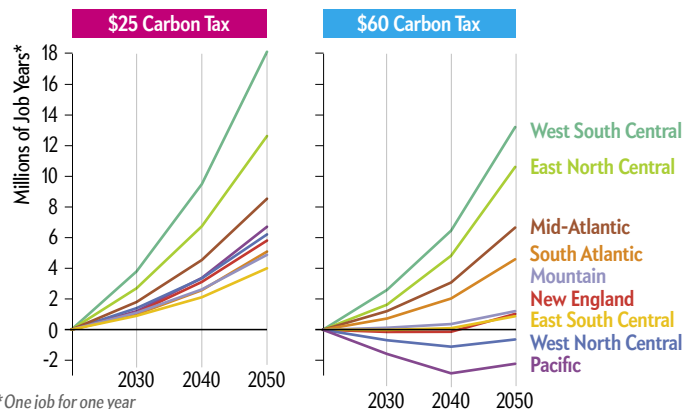
If the U.S. economy proceeds with “business as usual”—no carbon tax and no new energy regulations or policies—CO₂ emissions remain high or rise through 2050 in all sectors (top line in each graph). Under a \$25 or \$60 carbon tax, emissions drop significantly, especially in the power sector.



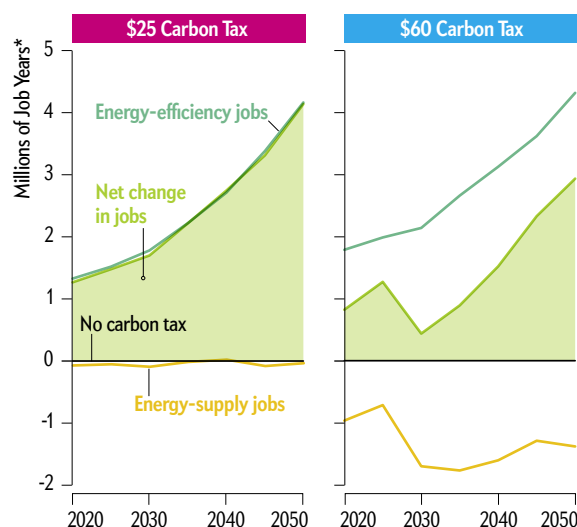
Jobs Go Up

Jobs by Region

A \$25 carbon tax would add an extra 72 million job years (one job for one year) across all nine U.S. Census divisions, compared with business as usual. A \$60 tax would also add jobs, though not as many; the Pacific and West North Central regions would see losses through 2040 before increases arise.



*One job for one year



Jobs by Type

Under a \$25 carbon tax, traditional energy-supply jobs, such as fuels or power generation, would decrease, but energy-efficiency jobs—construction, manufacturing—would more than compensate, creating a net gain (green area) of 4.2 million job years in 2050. A \$60 tax would cause greater supply-job losses, but efficiency-job gains would still produce a net increase.

SOURCE: “WOULD A GREEN NEW DEAL ADD OR KILL JOBS?” BY MARILYN A. BROWN AND MAJID AHMADI, SCIENTIFIC AMERICAN.COM, DECEMBER 19, 2019



Beyond Disruption:

The new age of healthcare and technology

Today's biopharma industry is seeing a level of therapeutic and curative transformation that would have been unimaginable just 10 years ago. What will the next 5, 10, 15 years bring for the biopharma industry and overall healthcare. How will the "mashup" that is underway between biopharma and digital medicine affect the C-suite, dealmakers, investors and the life science ecosystem as a whole?

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